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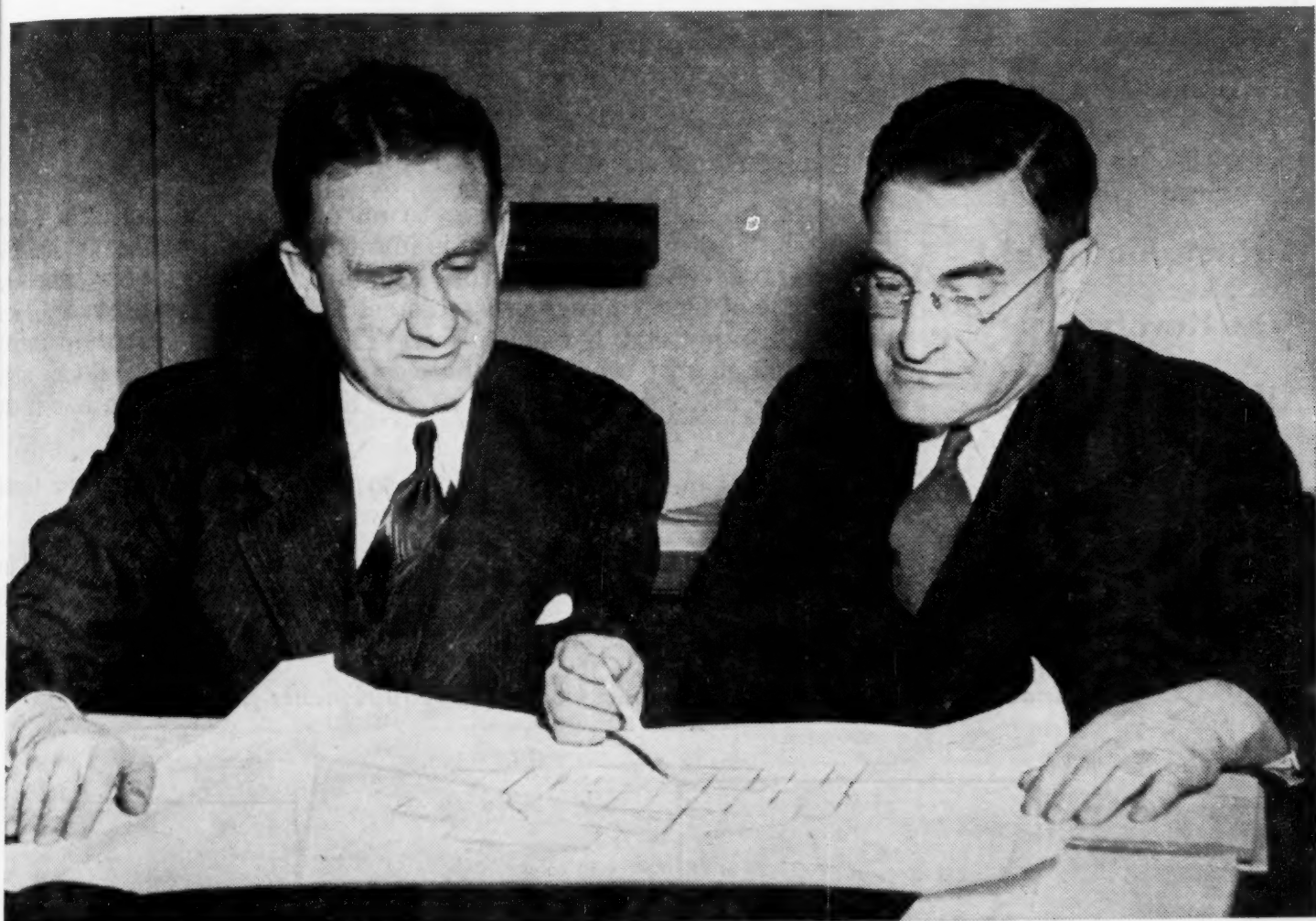
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# Science

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THE SCIENTISTS NEWSWEEKLY

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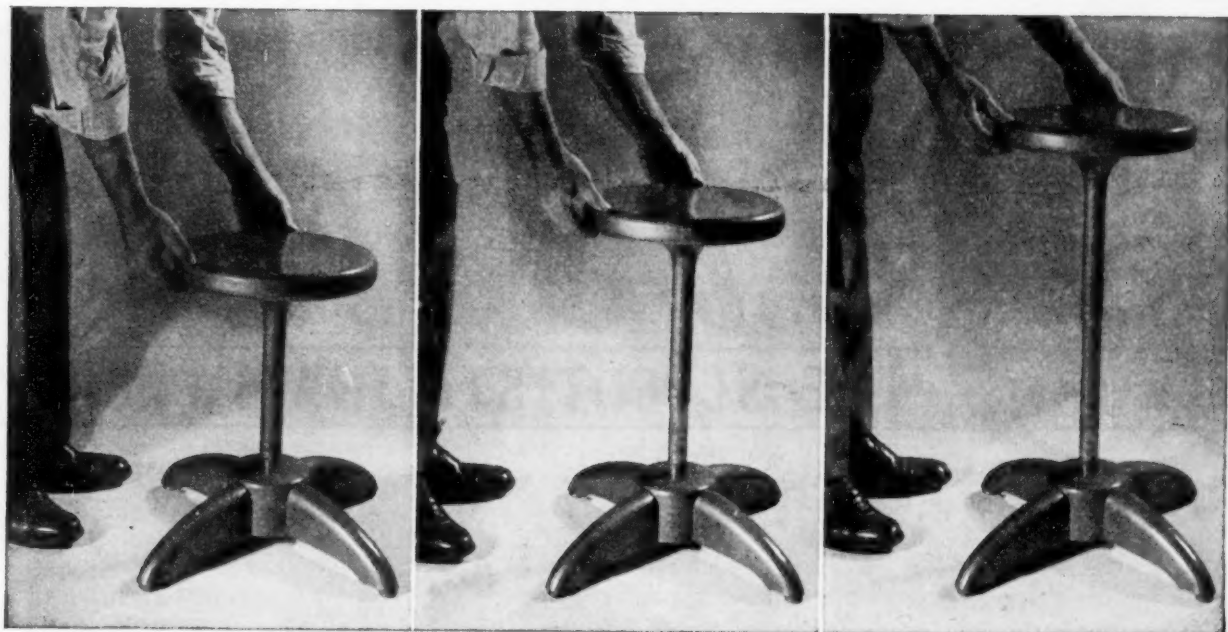
Walter H. Zinn, director of the Argonne National Laboratory, conferring with Farrington Daniels, chairman of the Board of Governors of the Laboratory, on the selection of the new site for a permanent location (*News and Notes*). Dr. Daniels is the chemistry adviser for *Science*.

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Mechanism of the Invasiveness of Cancer

Dale Rex Coman

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# Science

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# Mechanism of the Invasiveness of Cancer

Dale Rex Coman, *Department of Pathology,  
University of Pennsylvania Medical School, Philadelphia*

**D**URING THE LAST SEVERAL YEARS AN attempt has been made in this laboratory to arrive at an explanation of the invasiveness characteristic of malignant tumors. In contrast to benign tumor cells, which remain restricted to their site of origin, malignant cells have the ability to infiltrate adjacent tissues and thus become locally disseminated. Furthermore, their capacity for invasiveness allows them to penetrate into the lumina of lymphatic and blood vessels, whereby they are transported to more distant parts. It was thought that physical and chemical differences must exist between benign and malignant neoplastic cells which permit the former to remain localized and the latter to permeate adjacent normal tissues.

Under the assumption that these differences between the types of cells were ascertainable by experimental methods, a series of investigations was made.<sup>1</sup>

## THE DECREASED ADHESIVENESS OF CANCER CELLS

It was demonstrated by the writer (*Cancer Res.*, 1944, 4, 625) that attached pairs of cancer cells could be separated from each other by micromanipulation, through the application of much less force than was required to separate normal or benign tumor cells. The mutual adhesiveness of the cells was determined by measuring the bend produced in a previously calibrated micro-needle when subjected to the strain of detaching one cell from another. Thus, it was found that the mean force required to separate 50 pairs of normal squamous epithelial cells obtained from the lip was 1.42 mg. Similarly the value of adhesiveness for cells from skin papillomata (benign tumors) was 1.25 mg. On the other hand, the mean force necessary to separate 50 pairs of cells from squamous cell cancers of the lip was only one-third this value, or 0.47 mg.

This physical difference between cells of malignant and benign tumors composed of squamous epithelium affords the first requisite for an understanding of invasiveness. It is difficult to visualize any mechanism of invasiveness if tumors are composed of tightly adherent compact masses of cells. However, if the cells are but feebly attached to one another, facilitating complete separation, such separated cells are free to wander into adjacent parts by ameboid movement.

<sup>1</sup>This investigation was aided by a grant from the Cancer Research Division of the Donner Foundation, Inc.

Attempts were then made to find a chemical explanation of reduced adhesiveness. Normal squamous epithelial cells were subjected to various alterations in the chemical composition of the medium in which they were immersed while their adhesiveness was measured. In this way it was shown that absence of calcium from the medium caused reduction in adhesiveness of the cells (*Cancer Res.*, in press). For example, the mean force required to separate 100 pairs of cells in balanced salt solution was 1.34 mg., whereas the value for cells in calcium-free salt solution was only 0.96 mg., a significantly lower value. In this instance, as stated, calcium was absent from the medium surrounding the cells. In another experiment, methylcholanthrene, a substance shown by C. Carruthers and V. Suntzeff (*Science*, 1944, 99, 245) to reduce the calcium content of epithelial cells directly, was applied to the cells and their adhesiveness measured. Under these conditions also, adhesiveness was reduced.

Since it has also been shown by A. Brunschwig, L. Dunham, and S. Nichols (*Cancer Res.*, 1946, 6, 233) that cancerous tissue is abnormally low in calcium, and since the investigations just reviewed indicated that adhesiveness of normal cells was decreased when calcium was lowered experimentally, it was concluded that the decreased adhesiveness of cancer cells of the squamous epithelial variety is dependent upon their low calcium content.

## THE AMEBOID MOVEMENT OF CANCER CELLS

A satisfactory chemical basis for the separation of cancer cells from each other having been found, the only additional requisite for invasiveness is the ability of the detached cells to move; that is, if the cells, no longer bound to each other, are capable of ameboid movement, their penetration of the adjacent tissues is understandable.

In a previous investigation in this series (*Cancer Res.*, 1942, 2, 618) epithelial cells from human carcinomas were observed in tissue culture. It was found that individual cells frequently became detached from outgrowing sheets or clusters of epithelium and, further, that these detached cells were actively ameboid. Cells were seen to progress, in this way, some distance from the cluster from which they were derived and, by their proliferation, to build up new colonies. These observations confirmed earlier reports by W. H. Lewis and G. O. Gey (*Johns Hopk. Hosp. Bull.*, 1923, 34, 369) of

ameboid movement in cells from both sarcomas and carcinomas.

Thus, it can be regarded as established that, once cancer cells have become detached, they are capable of ameboid motion.

#### THE ROLE OF SPREADING FACTORS

The detached ameboid malignant cell is physically adapted to invasion of surrounding tissues. However, invasion would be facilitated further if the normal tissues were made more permeable to the cancer cells. This suggested the hypothesis that malignant tumors contain spreading factors, such as hyaluronidase, which, by softening the intercellular cement substance of adjacent normal tissues, render these tissues more susceptible to penetration by the cancer cells (*Amer. J. med. Sci.*, 1946, 211, 257).

Experiments designed to test this hypothesis were of two kinds. First, an analysis of human tumors was made to determine whether they contained significantly greater amounts of spreading factors than did normal tissues (*Cancer Res.*, in press). Extracts were made from a variety of normal and tumor tissues by grinding, freezing, and thawing the tissue and extracting it with sodium acetate. The acetate extract was used for the assay of spreading factor.

Two methods of assay were employed. By one method, the effect of the tissue extracts upon the spread of hemoglobin in the rabbit skin was determined. The other method depended upon measuring the reduction in viscosity of hyaluronic acid, the substrate upon which the enzyme, hyaluronidase, acts. By these methods it was found that several of the malignant tumors examined did contain spreading factors. In most instances the spreading factor content was not great, and in some it was lacking. When considering the presence of spreading factors in malignant tissues, it must be emphasized that the source of the spreading factors within the tumors has not been determined. It is possible that hyaluronidase was present in certain tumors because of infection by bacteria which were the source of the enzyme. If this is the only source of hyaluronidase in malignant tissue, then its presence is coincidental, even though it conceivably operates to facilitate invasion by the tumor cells by rendering the adjacent tissues more susceptible to penetration. It has yet to be demonstrated that the cancer cell itself contains hyaluronidase. Regardless of the ultimate source of the spreading substance, our analysis of human tumors revealed, in several instances, significant amounts obtainable from the tumors, so that support is lent to the hypothesis that spreading factors may facilitate the invasiveness of cancer cells.

In the second set of investigations, hyaluronidase was injected into transplantable sarcomas in mice, and into virus-induced papillomata in rabbits (*Cancer Res.*, in

press). The object of these *in vivo* experiments was to determine whether an excess of hyaluronidase would increase the invasiveness of tumors. The mouse sarcomas were invasive and metastasized to the lungs. It was thought that if hyaluronidase increased the invasiveness of these sarcomas, there would be earlier fixation of the tumors to the adjacent normal tissues and an increased frequency of pulmonary metastases. Neither indication of augmented invasiveness was demonstrable. The rabbit papillomata are primarily benign tumors which may become malignant in some instances when allowed to grow for a long time. It was thought that local injection of hyaluronidase might increase the incidence of malignancy, as judged by invasiveness and distant metastases. Again, confirmative evidence was not obtained. The negative results in these experiments force the conclusion that spreading factors of the hyaluronidase type, though they may be found in malignant tumors, are not essential to invasiveness. The mouse tumors, for instance, were strongly invasive to start with, and their invasiveness apparently could not be enhanced by an excess of hyaluronidase experimentally introduced.

In these *in vivo* experiments, in which spreading factor was injected into the animals daily over long periods, the formation of antienzymes must be considered. Such antienzymes, which inhibit the action of the enzyme on its substrate, have been reported by E. Haas (*J. biol. Chem.*, 1946, 163, 63, 89, 101), and it will be necessary to await further developments in this field before better-controlled experiments can be designed.

The concept of invasive growth that has resulted from the experiments summarized above depends upon a triad of factors:

- (1) Decreased adhesiveness of cancer cells, dependent upon local calcium deficiency. Decreased adhesiveness facilitates the separation of cells from each other so that they become detached units.

- (2) Ameboid movement, by which the malignant cells are enabled to wander into the surrounding parts to establish new colonies.

- (3) Liberation of spreading factor (hyaluronidase), which acts upon adjacent normal tissues. Hydrolysis of the hyaluronic acid of the intercellular cement substance of connective tissue opens the tissue spaces for penetration by the malignant cells. It is quite possible that this third factor is not requisite for invasive growth, but that when it does operate, it augments the facility with which invasion occurs.

Of the three factors the first two are of greater importance for invasive growth. It is of interest in this regard that the most invasive of all normal cells, macrophages, polymorphonuclear leucocytes, and lymphocytes, are all detached cells, rarely showing any evidence of mutual adhesiveness and all having great ameboid activity. The cancer cell possesses these same attributes, coupled with its capacity for unlimited proliferation.

# Artificial Radioactive Tracers:

## Applications to Chemistry and Medicine

Glenn T. Seaborg

University of California, Berkeley

ABOUT 450 INDUCED RADIOACTIVITIES are now known, there being at least one radioactive isotope for each of the elements of atomic numbers 1 to 96, inclusive. The work in connection with the Plutonium Project of the atomic bomb development has given rise to vastly superior methods for the large-scale production of a number of these isotopes and, in particular, a number of the most important ones. The outlook at the present time, therefore, is a very optimistic one, with almost unlimited possibilities for research. It is not at all out of the question that the greatest gains to humanity from the atomic energy development will result from the widespread use of tracers to solve a multitude of problems rather than from the harnessing of the power itself.

The present discussion will be concerned entirely with the induced radioactivities, because these now far surpass in importance the natural radioactivities for application in the atom-tagging field. The natural radioelements have been used as indicators or tracers in physical and chemical investigations for about 35 years, the first experiments having been performed by G. Hevesy and F. A. Paneth, but these early investigations were limited to those few elements which have naturally occurring radioactive isotopes. After the discovery of artificial radioactivity, the principle of investigation by "atom tagging" was extended at once to these new activities.

Immediately following the discovery of artificial radioactivity, a large addition to the list of radioactivities was made during 1934 and 1935 as the result of the work of E. Fermi and his associates, who produced unstable isotopes by neutron bombardment of the elements. Also, many radioactivities were produced by several other groups of workers, mainly as the result of bombardment with high-speed charged particles from artificial sources—in particular, bombardment with high-speed charged particles such as protons and deuterons, which were accelerated in various types of high-voltage apparatus.

Following this early work with these many types of particle acceleration apparatus and until recently, the main source for the production of radioactivities was the cyclotron, the use of which added hundreds of iso-

topes to the total and resulted in the production of very intense radioactivities. However, this did not result in the transmutation of weighable amounts of isotopes.

### THE URANIUM PILE

The recent accomplishment of the self-sustaining nuclear reaction in uranium marks another milestone in the field of artificial radioactivity. In addition to producing new isotopes, the chain-reacting units have increased by many orders of magnitude the amounts of the radioactivities which can be made available. As is now well known, the uranium chain-reacting units, called "piles," have given rise to the transmutation of elements on a weighable scale—in fact, on a scale not only of micrograms, milligrams, or grams but even of kilograms in some cases.

The fission product elements, *i.e.* the radioactive isotopes in the region of atomic numbers about 35 to 60, inclusive, are available in tremendous amounts. The pile, as a powerful neutron factory, also makes it possible to produce important amounts of practically any radioactive isotope which can be produced by neutrons; and, since almost all the important known isotopes can be produced by neutron irradiation, this means that in the future practically all such isotopes should be available in huge intensities. In a recent announcement from the headquarters of the Manhattan Project it was disclosed that a large number of such radioisotopes are now available for distribution to research men through qualified research institutions. A complete description of the available isotopes, their method of production, and the form and quantity in which they are available, together with a description of the organization for their allocation and distribution has been published (*Science*, June 14, 1946).

In the near future there will also be available other devices which will give rise to other milestones in the field of transmutation. Among these are the betatron and the synchrotron, with which it will be possible to accelerate electrons to the energy region of hundreds of Mev and, hence, to produce electromagnetic radiation of this energy. Also, the new 184-inch giant cyclotron at the University of California, Berkeley, is ready for operation. Using the new frequency modulation principle in order to compensate for the relativistic increase in mass at these tremendous energies, this instrument generates

Based on an address delivered before the Conference on the Future of Nuclear Science, Princeton University Bicentennial, September 24, 1946.

deuterons at 200 Mev and helium ions at 400 Mev of energy. These instruments should give the means for further study of fundamental particles, such as the mesotron, for production of new fundamental particles, and give rise to entirely new nuclear reactions. For example, from nuclei which have been bombarded with particles and radiation of this energy, there will come a literal shower of neutrons and protons—for example, a dozen or more at a time—and possibly in some cases even nuclei with mass below that of the heaviest region will undergo fission and give rise to their own groups of fission products. The use of these instruments will undoubtedly add to the list of induced radioactivities.

#### ARTIFICIAL ELEMENTS

One of the most important and interesting uses to which artificially induced radioactive isotopes have been put has been the investigation of the properties of those elements which do not exist in nature. In most cases so far, this type of chemical investigation has used a "tracer" technique (see *Science*, October 25, 1946, p. 379). The most spectacular examples of its application lay in the discovery and study of the chemical properties of new elements nonexistent in nature, *i.e.* the trans-uranium elements of atomic numbers 93, 94, 95, and 96. Element 93 (neptunium) was discovered in May 1940; element 94 (plutonium), late in the same year (see *Science*, October 25, 1946, pp. 379–380). In the case of plutonium, a long and complex process for its separation from uranium and fission products was to a considerable extent worked out before anyone had ever seen any plutonium even under the microscope. These studies have also led to the elucidation of the electron structure of the heaviest elements, the evidence indicating that these form a series of actinide elements, the added electrons for most of the 14 successive elements starting with thorium going into the 5f, an inner electron shell, similar to the addition of successive electrons to the inner 4f shell in the case of the 14 previously known lanthanide earths.

The experiments of Seaborg, R. A. James, L. O. Morgan, and A. Ghiorso in the Metallurgical Laboratory at the University of Chicago have recently led to the identification of isotopes of elements 95 (americium) and 96 (curium), making it possible to study the chemical properties of these elements by the tracer technique.

In the meantime it has been possible to produce neptunium and plutonium in weighable amounts in the chain-reacting piles. The isotopes which have been produced in this manner are the neptunium isotope of mass 237 and the famous plutonium isotope of mass 239, which is so important in the atomic energy field. With these it has been possible, using the methods of ordinary chemistry, to extend greatly the knowledge of the chemical properties of these elements.

There are also a number of lighter elements which are

now known to be extremely rare or nonexistent in nature but whose chemical properties have, nevertheless, been rather well defined as the result of their production by artificial means and the investigation of their properties by the tracer technique. Many experiments have been performed with unweighable amounts of these elements, which have atomic numbers 43, 61, 85, and 87.

C. Perrier and E. Segrè were able to show in 1937 that the deuteron bombardment of molybdenum produces radioactive isotopes of element 43, and they used these to study its hitherto unknown chemical properties. This is particularly interesting from an historical point of view because this is the first of the artificial elements to be discovered. Their experiments showed that the chemical properties resembled those of the heavier homologue, rhenium, to a much greater extent than they resembled those of manganese, the lighter homologue. These investigators used rhenium as carrier for the radioactivity in order to show that element 43 is precipitated by hydrogen sulfide from alkaline or acid (less than 10 *N*) solution. They investigated other properties, including the volatility of the oxide and chloride and the conditions for the electrolytic deposition of the metal. Recently R. P. Schuman and also D. C. Lincoln and W. H. Sullivan, working on the Plutonium Project of the Manhattan District, have independently observed the radioactivity (with very long half-life) due to the lower isomeric state of  $43^{99}$ , formed in the fission of uranium. This is interesting because it is now possible to isolate this isotope in weighable amounts. This particular isotope of element 43 was discovered by Segrè and Seaborg, who produced it from the deuteron and neutron bombardment of molybdenum and found that the upper isomeric state has a half-life of 6.6 hours and the lower, one of more than 40 years. The discoverers, Perrier and Segrè, have suggested the name "technetium" (Tc) for element 43, and it seems certain that this name and symbol will be adopted.

A radioactive form of element 61 has been positively identified in the experiments of J. A. Marinsky, L. E. Glendenin, and others, on the Plutonium Project of the Manhattan District, who found that isotopes  $61^{147}$  and  $61^{149}$ , with half-lives of about 3.7 years and 47 hours, respectively, are formed in the fission of uranium. This element is a rare earth, and the chemical experiments on the tracer scale show that its behavior is very similar to that of the preceding element, neodymium. Experiments involving selective adsorption and elution on ion-exchange resins led to the unambiguous separation of the element from its neighbors. The availability of isotope  $61^{147}$  in large amounts from fission makes it now possible to isolate the missing element 61 in weighable amounts, and I am confident that this will soon be done. The name which is to be eventually adopted for element 61 should be, and presumably will be, the one which Marinsky and Glendenin will suggest.

The discovery of radioactive element 85 (isotope  $85^{211}$ )

from bismuth plus 32-Mev alpha-particles, by D. Corson, R. Mackenzie, and Segrè, made it possible for these workers to investigate its properties. The general behavior is that of a metal, with little resemblance to the other halogens. It is precipitated by hydrogen sulfide in 6*N* hydrochloric acid solution with various carriers, and the sulfide is insoluble in ammonium sulfide. Volatility at comparatively low temperatures is observed; a piece of bombarded bismuth loses most of the activity before melting (275°C.). There is no precipitation upon the addition of silver nitrate to a dilute nitric acid solution using iodide as carrier. These investigators have given the name "astatine" (At) to this element.

A radioactive form of element 87 resulting from the alpha branching decay of actinium has been discovered by M. Perey in France. This isotope, given the name AcK, has the mass 223 and decays by negative beta-particle emission with a half-life of about 21 minutes. The experiments of Perey have shown that the element behaves, as expected, like a heavy alkali metal; for example, it is carried by the compound, cesium perchlorate. Perey has given it the name "francium" (Fa).

Perhaps the most extensive application of the artificial radioelements in chemical work has been to the study of "exchange reactions." In exchange experiments the atoms of an element in one of its valence forms or types of chemical combination are labeled by admixture with some radioactive isotope of the element which is of the same form or chemical combination. To this system is added the element in another state of valence or form of combination, containing none of the radioactive isotope; the presence of radioactivity in this second chemical form, after it has been separated from the first, shows that an effective exchange of atoms between the two different states of the element has taken place. Experiments of this type give information on chemical bond types, the strength and reactivity of chemical bonds and the effect of solvents on these properties, the structure of ions and compounds, the mechanism of reactions, and the mechanism of catalysis. In addition, exchange reactions often offer an excellent and convenient method for the introduction of radioactive atoms into compounds.

The subject of exchange reactions is too complicated to make possible accurate, complete generalizations. It seems profitable, however, to make a few rough statements concerning homogeneous exchange reactions. If we consider exchanges of a given element between two sorts of molecules or ions in which it is held by electron-pair bonds to different numbers or kinds of other atoms, we may say in general that such exchange reactions do not proceed with appreciable rates except in those cases where there are reversible reactions which enable the exchanging atoms to reach equivalent states of chemical combination. For example, there is no exchange of atoms between phosphate and phosphite ions, sulfate and

sulfite ions, sulfur and carbon disulfide, iodide ion and iodoform, etc. On the other hand, exchanges have been found between chloride and chlorate ion (due to the oxidation-reduction equilibrium), between lead nitrate and lead chloride (an extreme example of the ionization exchange mechanism), and between iodide ion and iodine (through the formation of a symmetrical intermediate,  $I_3^-$ ). When the two exchanging molecules differ only in their net charge, another exchange mechanism—the transfer of an electron from one to the other—may become possible. For example, exchanges have been observed between  $Fe^{++}$  and  $Fe^{+++}$  and between  $MnO_4^{--}$  and  $MnO_4^-$ . It is no doubt true that some exchanges occur through a simple transfer of atoms between molecules during a collision; such a mechanism is a special case of exchange through the formation of an intermediate. In many cases the observation of exchanges of this sort suggests the existence of unstable intermediates which might not be known from other reaction studies.

Probably the most important isotope from the standpoint of future possibilities is the radioactive  $C^{14}$ . This isotope, discovered by S. Ruben and M. D. Kamen at the University of California, has a half-life of some thousands of years and therefore, before the advent of the chain-reacting pile, was practically unavailable due to the difficulty of its production in the large amounts needed to produce substantial radioactivities. However, the intense neutron source in the piles makes it possible now to produce  $C^{14}$  in such quantity and high specific activity as to place it in a class along with the most available and suitable isotopes. It can be produced in either of two ways: the neutron irradiation of carbon, preferably enriched  $C^{13}$ , by the reaction  $C^{13}(n,\gamma)C^{14}$ , or the neutron irradiation of nitrogen by the reaction  $N^{14}(n,p)C^{14}$ . Both of these reactions take place with slow neutrons. The reaction with nitrogen is, of course, preferable from the standpoint of producing  $C^{14}$  of the highest specific activity, it being, in fact, possible to produce isotopically pure  $C^{14}$  in this manner. The radiation is of relatively low energy, making it necessary for its detection to employ instruments designed with this in mind, and, in the investigations, to pay close attention to the self-absorption problem.

A whole vista of opportunity is, of course, opened as a result of the availability of the  $C^{14}$  isotope. Organic chemists, biochemists, physiologists, and men of medicine have dreamed for years of the day when a radioactive isotope of carbon suitable for tracer investigations should become available. A few of the possibilities which have opened through its availability will be indicated presently, but this field is so vast that it is certain that the best ideas are yet to come.

A great deal has been said in comparison of the potentialities of radioactive  $C^{14}$  and the separated stable  $C^{13}$  in these fields. Actually, these isotopes complement each other, and it is very fortunate that both are avail-

able. There now exists the interesting possibility of tagging each of two different carbon atoms in a molecule or system and then *simultaneously* observing the course of each. Also, the separated  $C^{13}$  makes possible the production of radioactive  $C^{14}$  of higher specific activity from the reaction  $C^{13}(n,\gamma)C^{14}$ .

Another isotope which has great potentialities is the radioactive  $H^3$ , which has a half-life of about 30 years. This can be used in many of the ways indicated for the use of  $C^{14}$  if it is present in a molecule in a nonlabile position. The availability of the intense neutron sources makes possible its production in weighable amounts by means of the reaction  $Li^6(n,\alpha)H^3$ . The radiation consists of extremely low-energy beta-particles, and therefore its detection demands the use of very special instruments, it being necessary to introduce the material in the form of a gas into the inside of the Geiger-Müller counter, ionization chamber, or electroscope.

Besides radioactive  $C^{14}$  and  $H^3$ , such isotopes as the 14.3-day  $P^{32}$ , the 87-day  $S^{35}$ , the 180-day  $Ca^{45}$ , the 47-day  $Fe^{59}$ , the 250-day  $Zn^{65}$ , the 53-day  $Sr^{89}$ , the 8.0-day  $I^{131}$ , and many others have offered and will offer many opportunities for important research.

The first and most obvious application in organic chemistry for  $C^{14}$  would be in an examination of the mechanisms of many isomerizations and rearrangements of organic molecules. There are a number of reactions in which carbon atoms or groups of carbon atoms move from one part of a molecule to another, and the question of just how this migration is accomplished has been a subject for discussion among organic chemists for many years. By labeling the migrating groups in certain positions it should be possible to determine the precise sequence of events in such a reaction. In many types of rearrangements it is impossible to tell, by ordinary means, which carbon atoms are actually migrating. It is easy to see how, by a selective labeling of atoms, an unequivocal answer to these questions is obtained.

Not only is this type of information of interest for itself and the light it will throw upon the behavior of organic substances, but it is a necessary preliminary to the synthesis of tagged compounds of biological interest and to the examination by degradation of metabolic products derived from administered labeled materials.

It is in this latter field of biochemistry that the carbon isotopes will have their greatest usefulness. The determination of the intermediary metabolism of the major structural and energy-transforming materials of living organisms such as fats, proteins, and carbohydrates, as well as the catalytic or organizing substances such as vitamins, hormones, and enzymes, will undoubtedly make great strides as a result of the availability of isotopic carbon and some of the other isotopes as well.

Turning to biological systems, we find a virtually unlimited field of important work for the organic chemist and workers in all branches of biology.

It is not out of the question that a complete understanding of the photosynthetic mechanism might give men the ability to synthesize food and fuel at will, using this principle. This could give rise to a literal harnessing of the sun's energy. With the aid of  $C^{14}$  this might be accomplished. A number of experiments have been performed with the 21-minute  $C^{11}$ , but this short half-life placed definite limits on the extent of progress which was possible. Nevertheless, Ruben, Kamen, and W. Z. Hassid were able to use radioactive  $C^{11}$  in a study of photosynthesis in which considerable progress was made. Radioactive carbon dioxide was fed to the unicellular green alga, *Chlorella*, and also to higher plants under various controlled conditions in both the light and the dark. The results obtained so far have been quite interesting. The higher plants and the algae absorb carbon dioxide in the dark. This process takes place concurrently with the release of  $CO_2$  by respiration, so that the net effect is an evolution of carbon dioxide. Only by the tracer technique was it possible to demonstrate a simultaneous uptake and evolution of carbon dioxide. The dark uptake of carbon dioxide is very likely the first step in photosynthesis and can be represented by  $RH + CO_2 \rightleftharpoons RCOOH$ . Decarboxylation experiments have shown that the bulk of the radioactive carbon is in the carboxyl group. Attempts to identify the radioactive substances formed in the dark and in the light have been thus far unsuccessful. It is of considerable interest to note that formaldehyde, which has played a prominent role in many proposed mechanisms, was not identified from the radioactive carbon dioxide introduced. Experiments with the ultracentrifuge and diffusion methods indicate the average molecular weight of the radioactive molecules to be about 1,000, which explains the failure to identify them chemically with any small molecules.

The radioactive elements, in particular radioactive carbon, will, of course, receive widespread use in studying animal metabolism. In the highly intricate process of carbohydrate metabolism in man, present knowledge has been gained, for the most part, only as a result of painstaking analytical work by classical methods. In general these methods are not capable of high precision and are not adapted for the determination of highly labile compounds. Thus, it is quite likely that many important details of the process under investigation have not been revealed. Almost certainly, the use of radioactive tracers will bring these details to light. Aside from circumventing many analytical difficulties, the use of labeled elements can yield important information not possible by other methods. It is very often the case in biological systems that reactions proceed under steady-state conditions. With radioactive tracers it is possible to follow the formation of a compound in the presence of a considerable amount of the previously synthesized compound or to measure synthesis while the net reaction

constitutes breakdown. Such measurements will be of great value in determining the mechanisms of biological reactions. For example, B. Hastings and his collaborators at Harvard have used  $C^{14}$  in the study of glycogen formation in the liver and have found that the incorporation of carbon dioxide into organic molecules takes place here. Many carbon dioxide-incorporating reactions have been studied with  $C^{13}$  by H. G. Wood and C. H. Werkman. The present availability of  $C^{14}$  will make possible the elucidation of many mechanisms in the metabolism of carbohydrate and fat. Many biologists believe that artificial radioactivity has given biology and medicine what is probably the most useful tool for research since the discovery of the microscope, because almost all of the elements and compounds in biological systems can be tagged and their course through living systems studied.

The most simple and direct use of an element as a tracer is accomplished by its administration as a simple inorganic compound, in which case the distribution of the tagged element in the various structures of the plant or animal is determined by measuring the radioactivity of the samples of tissues and body fluids. A very large number of experiments of this type have been performed, principally to aid in the understanding of mineral metabolism. For example, the absorption of iron as related to anemia has been studied by G. H. Whipple and P. F. Hahn at the University of Rochester.

Radiophosphorus has been the most widely used of all the artificially prepared radioelements as a tracer for metabolic studies in biological systems. The distribution of administered phosphorus in human and animal tissues has been extensively studied. It has been observed, for example, that the retention of a single dose of disodium phosphate varied in different tissues in the following decreasing order: bone, muscle, liver, stomach plus small intestines, blood, kidneys, heart, lungs, and brain. In other experiments a selective accumulation of radiophosphorus in leukemic tissues was found to occur. This was important in that it indicated that the leukemic tissues could be subjected to a greater degree of beta-particle irradiation than the normal tissues, which in turn indicated the application of radiophosphorus as a potentially valuable therapeutic agent.

The synthesis of the biologically important organic phospholipids has been studied by G. Hevesy and co-workers in Copenhagen and I. L. Chaikoff and his associates in California. Compounds like these are now considered to be vital links in the complex, low-temperature oxidation mechanisms characteristic of living systems. Chaikoff and associates have shown the importance of the liver in such synthesis and transport: how the turnover of these substances through the liver can be altered by the administration of choline and certain amino acids and how newly synthesized molecules are absent altogether from the blood when the liver is removed. Using surviving tissue slices, they have demon-

strated the dependence of the synthesis upon the proper functioning of certain respiratory enzyme systems. The first real insight into the mechanism of the action of insulin on carbohydrate metabolism has come from studies, by J. Sacks at Michigan with  $P^{32}$ , on the effect of this hormone on the turnover of phosphorus compounds in muscle. All of these studies, of which only a few were mentioned, would have been impossible without the use of a labeling agent.

Extensive metabolic studies have been made with the use of radioactive iodine as an indicator. The pioneering work in this field was done by S. Hertz and his co-workers in Boston and J. G. Hamilton and co-workers at California. The thyroid gland, through its synthesis of the iodine-containing hormone, thyroxine, controls the metabolic rate of the entire organism. Nevertheless, the quantities of iodine compounds produced and distributed are so small that even the finest micromethods are hardly adequate for the task of studying these processes. With the use of radioactive iodine the analytical difficulties can be largely overcome, and, in addition, types of measurements can be made which are not possible from chemical analysis. Among these is the measurement of the uptake of orally administered radioiodine by the intact thyroid glands of normal human subjects and by those of patients suffering from various types of thyroid disorder. The course of the uptake may be followed simply by placing a Geiger counter in the vicinity of the throat. The thyroids of patients with hypothyroidism were shown to accumulate iodine at a slow rate, while there was a relatively large uptake of administered iodine in the thyroid glands of patients with nontoxic goiters. In contrast to these behavior patterns, the thyroids of patients with hyperthyroidism were shown to take up administered radioiodine at a remarkably rapid rate and also to discharge the iodine from the gland in a rapid fashion. It is seen from these studies that an aid toward diagnosing the condition of the thyroid gland is available.

A large amount of work on iodine metabolism has been done by Chaikoff, I. Perlman, and M. E. Morton at the University of California. They were able to follow in some detail the distribution of organic iodine compounds from the thyroid gland through the blood to peripheral tissues in various states of thyroid activity; to demonstrate that, to a limited extent, tissues other than the thyroid gland are able to synthesize thyroxine; and, by using isolated surviving tissues, to tie in the synthesis of an organic compound with the energy-producing enzyme systems.

B. C. Smith and E. H. Quimby at Columbia have used the gamma radiations from intravenously injected  $Na^{24}Cl$  to determine the rate of passage of sodium into the extracellular phase of the tissues in cases of peripheral vascular disease and thus determined the competency of the circulation—another example of use for diagnosis.

Many more possibilities for the use of radioactive

isotopes in biochemical and physiological work might be suggested, but those given above are typical.

The study of the mechanism of action of antibiotic substances, many of which act by means not completely understood at present, will be possible. For example, the synthesis of radioactive penicillin or streptomycin might give rise to a method for investigating the mechanisms by which these great substances operate. The mechanism of action of antibodies might also be investigated by the use of tracers.

Another possible use of tracers is, of course, in the study of cancer. Here, in addition to the possibilities cited in connection with the use of radioactive indicators in the investigation of mechanisms, there is the therapeutic possibility of effecting the selective deposition of the radioactive material in the cancerous tissue, as has been mentioned in the case of leukemia. It has occurred to many investigators that it should be possible in the future to synthesize some compound containing a radioactive substance, this compound having the property of being selectively absorbed by the cancerous tissue so that the radioactive rays can act directly at this spot without harmful effects on the body's healthy tissue.

Another possibility, which may sound quite startling, is that of tagging bacteria with radioactive  $C^{14}$ . This appears to be feasible and to open great possibilities in the study of disease. In fact, Chaikoff and A. Kaplan have made a beginning by tagging the tuberculosis bacillus with radioactive phosphorus in some experiments which have not yet been brought to completion.

In addition to the therapeutic uses of radioactive substances which have already been mentioned, therapeutic value has been established in the work of J. H.

Lawrence and associates, who have had some success in the application of radioactive  $P^{32}$  to the temporary control of the blood diseases, polycythemia vera and leukemia. A large number of other therapeutic uses will surely be found, since it will be possible to apply alpha-particles, beta-particles, and gamma-rays to this purpose. It is worth pointing out that all of these radiations are represented in isotopes which can be produced in quantity, so that it is quite likely that the use of radium and its descendants in this type of therapy will soon be superseded by the artificial radioactive elements.

Availability of large quantities of radioactivities has also opened the possibility of their use in industry and industrial processes. Radioactive indicators may soon be used to follow the course of products and impurities in large industrial processes. Applications should be found in the testing of the efficiency of distillation apparatus, in testing for leaks, and in many other ways. The intense sources of gamma-rays will find application in the field of radiography, in looking for imperfections in metal products, studying the path of fast-moving parts, etc.

With respect to chemical problems of direct interest to industries, many examples could be cited. Among these may be mentioned studies, with  $C^{14}$ , of the mechanism of catalytic cracking, isomerization, and alkylation of hydrocarbons, which are of profound interest to the oil industry.

The future seems to hold unlimited possibilities for the application of radioactive tracers to scientific problems. It is certain that the applications made thus far are just the beginning of what is going to become an extremely large and successful field of research.

### Local Committees, Chicago Meeting, AAAS

From April 7 to 9 officers of the AAAS will meet with representatives appointed from the various educational and cultural institutions in the Chicago area to serve on five committees that will direct local preparations for the 114th meeting of the AAAS, to be held in Chicago December 26-31, 1947. These committees, of about 12 members each, will handle problems of reception and entertainment, procurement and distribution of equipment, registration, and publicity, and will help to raise funds to defray expenses incurred by the work of the local committees.

Honorary chairmen, serving in an advisory capacity for the local committees, include: Paul M. Angle, secretary, Chicago Historical Society; Charles C. Caveny, dean, Chicago Undergraduate Division, University of Illinois; Walter H. Chute, director, John G. Shedd, aquarium; H. C. Coffman, president, George Williams College; V. R. Edman, president, Wheaton College; H. K. Gloyd, director of Museum, Chicago Academy of Sciences; Clifford C. Gregg, director, Chicago Natural History Museum; Henry T. Heald, president, Illinois Institute of Technology; Robert M. Hutchins, chancellor, University of Chicago; A. C. Ivy, University of Illinois; Paul A. Jenkins, executive secretary, Chicago Technical Societies Council; K. Richard Johnson, head of Science Department, National College of Education; T. Lehmann, president, Elmhurst College; L. R. Lohr, president, Museum of Science and Industry; Lee Medsker, dean, Wright Junior College; Comerford J. O'Malley, president, De Paul University; Franklyn B. Snyder, president, Northwestern University; Edward J. Sparling, president, Roosevelt College.

The Chicago Convention promises to be one of the largest on record. At least 60 affiliated and associated societies and sections are planning to meet with the Association.

# NEWS

## and Notes

A new location for the Argonne National Laboratory for research and development in atomic energy, and acquisition of 3,645 acres of land in Du Page County, Illinois, were approved recently by the U. S. Atomic Energy Commission. The site is approximately 26 miles southwest of the center of Chicago, and 4 miles west of facilities of the Laboratory in the Palos Area of Cook County Forest Preserve.

Argonne National Laboratory was established for research and development in all phases of atomic energy,

is chairman, chose Chicago as the permanent site because of its geographical location and transportation advantages.

Prime consideration in the search for a permanent location was engineering features of the land. Topography, prevailing meteorological conditions, type of foundation, and available water, sewage, and power facilities were considered, and the Du Page County site was the only area investigated which satisfied all requirements. In addition, its proximity to the present Forest Preserve site will allow maximum use of facilities there during the transition period.

"Construction plans for the permanent buildings of the Argonne National Laboratory," Walter H. Zinn, director, said, "call for some 12 major buildings to house administration; physics, chemistry, biology,

research institutions—reviews matters of general policy and makes necessary recommendations for submission to the Contractor and the Government. A representative from each of the 25 participating institutions serves as a member of the Council.

The participating institutions are: Battelle Memorial Institute, Carnegie Institute of Technology, Case School of Applied Science, Illinois Institute of Technology, Indiana University, Iowa State College, Mayo Foundation, Michigan State College, Northwestern University, Notre Dame University, Washington University, Western Reserve University, University of Chicago, University of Cincinnati, University of Illinois, University of Iowa, University of Michigan, University of Minnesota, University of Missouri, University of Nebraska, University of Pittsburgh, and University of Wisconsin.

### About People

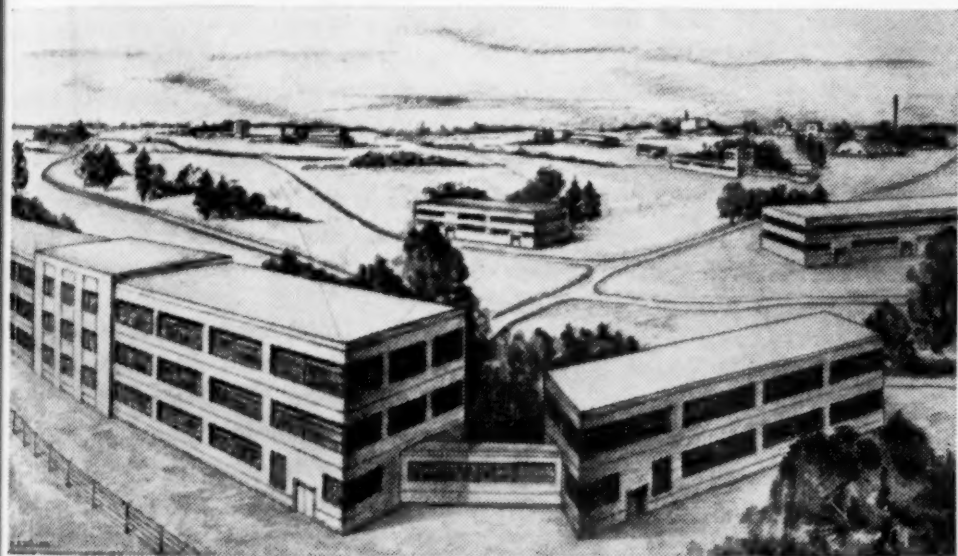
James B. Conant, president of Harvard University, delivered a special address to the staff and student body of the University of Texas Medical Branch, Galveston, February 21, on "The Growing Relations of Chemistry and Medicine."

C. L. Bird, lecturer in dyeing at Leeds University, England, has been appointed editor of the *Journal of the Society of Dyers and Colourists* to succeed F. M. Rowe, who died December 8 (*Science*, February 14). Mr. Bird was previously assistant editor of the journal.

Donald Wallace MacKinnon, professor of psychology, Bryn Mawr College, has accepted an appointment as professor of psychology at the University of California, Berkeley, beginning in September 1947.

Laurence H. Snyder, chairman, Department of Zoology and Entomology, Ohio State University, delivered the Marshall Woods Memorial Lecture at Brown University February 18, on "Human Genetics and Public Health."

Peter Gray, professor of biology, was named head of the Department of Biological Sciences, University of Pittsburgh, in February. He has been acting head since February 1946, when O. E. Jennings resigned to become director of the Carnegie Museum.



Artist's sketch of proposed facilities of the Argonne National Laboratory.

including fundamental research in physics, chemistry, biology, medicine, and engineering; the development of industrial power; and research on military uses.

Present facilities of the Laboratory are housed in four buildings on the campus of the University of Chicago, the Museum of Science and Industry, and the Palos Area of Cook County Forest Preserve. Operating difficulties due to wide dispersion of facilities were apparent early, and a permanent site was sought. The Board of Governors of Argonne National Laboratory, of which Farrington Daniels

medical and engineering research; nuclear reactors and allied equipment. Construction will be spread over a period of approximately three years."

Argonne Laboratory, one of a projected series of national laboratories, is successor to the wartime Metallurgical Laboratory of the Manhattan Engineer District. Its facilities are operated by the University of Chicago under contract with the Atomic Energy Commission. The Board of Governors of the Laboratory, comprised of 7 representatives elected by the Council of Participating Institutions—midwestern academic and

**L. Don Leet**, in charge of the Harvard Seismograph Station, was recently appointed professor of geology at Harvard University.

**I. S. Ravdin**, John Rhea Barton professor of surgery, University of Pennsylvania, will deliver the 14th E. Starr Judd Lecture April 15 at the University of Minnesota, Minneapolis, on the subject, "Changing Concepts in Surgical Care." The late E. Starr Judd, an alumnus of the University of Minnesota Medical School, established this annual lectureship in surgery a few years before his death.

**Harold H. Biswell**, in charge of range research, Appalachian Forest Experiment Station, Asheville, North Carolina, will join the Department of Forestry, University of California, Berkeley, in May.

**Harris M. Benedict** recently became senior plant physiologist and **Carl A. Taylor** became research agriculturist for the Natural Rubber Research Project at Salinas, California (*Science*, January 27, 1946). The work is being performed by Stanford Research Institute under contract with the Office of Naval Research as a fundamental study of the genetics and physiology of rubber-bearing plants.

**Henry S. Sharp**, Department of Geology and Geography, Barnard College, Columbia University, will spend about six months in Japan and the South Pacific Islands as geologist for the Military Geology Unit of the U. S. Geological Survey.

### Visitors to U.S.

**Honor B. Fell**, director of the Strangeways Laboratory, Cambridge, England, spent a week, beginning February 17, at the University of Texas Medical Branch inspecting research studies in the Tissue Culture Laboratory, which is under direction of Charles M. Pomerat. Dr. Fell also participated in developing special tissue culture techniques for the *in vitro* study of cellular enzyme and growth systems.

**Hsiiao-Chien Chang** and **Pao-Chang Hou**, dean of Hsiang Ya Medical College, Changsha, Hunan, China, and professor of pathology, Cheeloo University, Tsinan, China, respectively, were visitors at Duke University School of Medicine November 10-17. As guests of the U. S. State Department they will continue to

visit American medical institutions until June 1947. Dr. Chang addressed the undergraduate medical society on "Medical Education in China," and Dr. Hou lectured to the Duke faculty and student body on "Leprosy and Plague" and "Kala-Azar."

### Fellowships

**Socony-Vacuum Oil Company, Inc.**, New York, has announced an appropriation of \$20,000 to establish 10 annual \$2,000 fellowships in chemistry and physics at leading educational institutions.

For the next academic year the fellowships have been awarded to the California Institute of Technology, Harvard University, University of Illinois, Massachusetts Institute of Technology, University of Notre Dame, Ohio State University, Princeton University, Rice Institute, University of Wisconsin, and Yale University.

Recipients, who must have at least one year of graduate work, are not required to study subjects connected with the petroleum industry.

### Grants and Awards

**James Irvin Hoffman**, member of the chemical staff of the Bureau of Standards since 1919, was awarded the 1946 Hillebrand Prize in chemistry at a meeting of the Chemical Society of Washington, March 13. Dr. Hoffman was cited for the concept and demonstration of the use of ether in removing impurities from crude uranium, and also for work in a new process of alumina production. The Hillebrand Prize, established in 1925 in honor of William Francis Hillebrand, chief chemist of the National Bureau of Standards from 1908 to 1925, is made each year to a member of the Chemical Society of Washington who has made outstanding contributions to chemistry during the preceding three years.

**Pi Lambda Theta**, National Association for Women in Education, announces two awards of \$400 each to be granted again this year for research on any aspect of the professional problems and contributions of women in education or another field. Three copies of the final report of the completed research study should be submitted to the chairman of the Committee on Studies and

Awards, Bess Goodykoontz, U. S. Office of Education, Washington 25, D. C., before July 1.

**The Robert Gould Research Foundation** of Erlanger, Kentucky, has established 2 grants of \$1,500 for student training in nutrition and 10 grants-in-aid of research for 1947-48. The grants-in-aid of \$2,000 each will be distributed equally in the following fields: recognition of preclinical nutritional deficiencies; human nutritive requirements; most effective techniques for educating the public in nutrition; improvement in nutritive value of human food as grown; and improvement in the nutritive value of animal food.

Inquiries may be addressed to: Arthur Lejwa, Scientific Director, The Robert Gould Research Foundation, Inc., Cincinnati 2, Ohio.

### Colleges and Universities

**The California Institute of Technology**, Pasadena, has established the David Lindley Murray Education Fund with a gift of \$300,000 from Mrs. Katherine Murray, income of which will provide 15 scholarships. Mrs. Murray, with her husband, for whom the fund is named, had been a visitor to Pasadena from Illinois for many years prior to her death in 1944.

**The University of Michigan**, Ann Arbor, has granted sabbatical leaves of absence to A. D. Moore, professor of electrical engineering, in the 1946-47 spring semester, and Charles H. Griffiths, professor of psychology, in the 1946-47 second semester.

**Harvard University's engineering laboratories** are now testing samples of soil and rock from the Isthmus of Panama in connection with proposals for new canal facilities for ships passing from the Atlantic to the Pacific.

The University has started extensive engineering studies of canal problems in the area to determine the best means of providing for growth of interoceanic commerce and protecting the security of the Nation.

Plans for several locations and types of canals are under consideration, among them addition of a third set of locks to the present canal, conversion of the present lock canal into a sea-level canal, and proposal to dig a new sea-level canal in

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other part of the Isthmus. Selection of the plan, which will be presented to Congress before the end of 1947, will depend on tests to be performed within the next few months at the Harvard engineering laboratories.

Harald M. Westergaard, professor of civil engineering, Arthur Casagrande, professor of soil mechanics and foundation engineering, and L. Don Leet, seismologist and professor of geology, are now engaged in the Isthmian Canal studies. Dr. Casagrande, in charge of the laboratory testing work, has under him William L. Shannon, loaned to the University by the War Department, and Liang-sheng Chen, engineer, who received his Doctor's degree from Harvard. Dr. Leet will be concerned with the effect of earthquake and volcanic activity on any proposed canal structure and the effect of vibrations set up by explosions and their bearing on the angle of slope of canal cuts.

New testing chambers are under design which will subject samples of soil and rock to dynamic forces resulting from explosions of present-day weapons. Electronic measuring devices are employed in a testing chamber known as the triaxial compression apparatus for dynamic loads. A sample of the soil or rock is put into the chamber, which consists of a lucite cylinder with substantial metal ends. Above the sample is a proving ring attached to a piston which exerts a load on the sample. The amount of load reaching the sample is measured electronically through strain gages mounted on the proving ring, and similarly, the amount of deformation of the sample is measured electronically by strain gages on a cantilever beam mounted on the piston. The pressure within the chamber can be raised to simulate conditions at the depths within the earth from which the sample comes.

## Summer Programs

The Massachusetts Institute of Technology announces a special summer session in applied mathematics, from August 4 to September 19, in which the following graduate courses will be offered: Theory of Plates and Shells, by F. B. Hildebrand and E. Reissner; Theoretical Hydromechanics, by E. Reissner and C. C. Lin; Advanced Topics in Applied Mathematics, by J. L. Synge, H. Reissner, W. Prager, F. B. Hildebrand, and P. D. Crout; and Tensors in Mechanics, by D. J. Struik.

**The Biological Laboratory, Cold Spring Harbor, Long Island, New York**, is again offering a course for research workers by Mark H. Adams, of New York University. The course, designed to acquaint scientists with some of the techniques used in research with bacterial viruses and recent results of such work, will be held from June 30 to July 18.

**Brown University's Graduate Division of Applied Mathematics** will offer a special summer program of instruction in Modern Mechanics of Fluids and Solids with particular emphasis on nonlinear problems, July 7-August 30.

The session, open to advanced graduate students, instructors, and research personnel of government and industry, will consist of two periods, July 7-August 1, and August 5-30. During each period a course in fluid mechanics and another in mechanics of solids will be offered, each course consisting of 20 lectures and 12 discussion periods. Instruction will presuppose a good foundation in classical fluid dynamics and theory of elasticity.

Courses offered will be Dynamics of Viscous Fluids, by Chia-Chiao Lin, Brown University; Theory of Structural Stability, George Francis Carrier, Brown University; Dynamics of Compressible Fluids, Sidney Goldstein, University of Manchester, England; and Theory of Plasticity, William Prager, Brown University.

Inquiries should be addressed to the Registrar, Graduate School, Brown University, Providence 12, Rhode Island.

## Industrial Laboratories

**A pound and a half of potassium phthalimide containing the "tracer" isotope, Nitrogen 15**, and believed to be the largest quantity of an organic compound containing an isotope ever prepared was shipped recently from Rochester to Columbia University in New York.

According to C. F. H. Allen, assistant superintendent of Eastman Kodak's Synthetic Organic Research Laboratory, under whose direction the work was conducted, the Columbia group will convert the potassium phthalimide into special amino acids containing the isotopic nitrogen.

Kodak's concentration of isotopes, begun in 1940, is now being carried out on quite an extensive scale. The work will

gradually become a part of the production program which supplies about 3,000 chemical compounds to research laboratories in the United States.

Assisting Dr. Allen in the work on Nitrogen 15 were C. Vernon Wilson and Donald Burness, of the laboratory staff.

**Smith, Kline & French Laboratories**, Philadelphia, Pennsylvania, announces appointment of Charles H. Fahrenholz, Jr., Grove City College, and George E. Fajcsi, Ohio State University, to its research staff.

**The Chemical Research and Development Department, Armour and Company**, Chicago, announces appointment of Lawrence L. Lachat, senior fellow at Mellon Institute, Pittsburgh, to direct development of new biochemicals which have become available largely as a result of war-time research under contract between Armour and the OSRD.

**General Electric Company** on March 31 began shipment of the first 100,000,000-volt betatron to be built on a commercial basis. The machine is being built by the Company's General Engineering and Consulting Laboratory for Clinton Laboratories at Oak Ridge, Tennessee. Shipment of final components will be completed by midsummer.

The new instrument for Clinton Laboratories, operated by the Monsanto Chemical Company for the Atomic Energy Commission, will weigh approximately 160 tons, and will be 9 feet high, 6 feet wide, and 15 feet long. General Electric is building a similar instrument for the University of Chicago to be used for nuclear research.

## Meetings

**The Medical Library Association** will hold its 46th annual meeting in Cleveland, Ohio, May 27-29, at the invitation of the Cleveland Medical Library Association, with headquarters at the Wade Park Manor.

In addition to scientific sessions on May 27-28, a symposium, "Visual Aids and the Medical Library," will be held May 28. W. B. McDaniel, librarian of the College of Physicians of Philadelphia, will give the presidential address at the morning meeting, May 29.

**The Association of Southeastern Biologists** will hold its 8th annual meeting at Emory University, Georgia, April 18-19, with the southeastern section of the Botanical Society of America and the Southern Appalachian Botanical Club. All biologists in the Southeast are invited to attend.

**The Fifth International Pediatrics Congress** will be held July 14-17 at the Waldorf-Astoria Hotel, New York City.

The Congress, with L. Emmett Holt, Jr., Bellevue Hospital, New York, as general secretary, will consist of scientific discussions, a scientific exhibit, visits to medical institutions in New York, and a post-Congress tour. The scientific discussions will consist of 8 plenary sessions on nutrition, tuberculosis, alimentary toxicosis, virus diseases, chemotherapy, congenital heart disease, neonatal mortality, incompatibility of blood, as well as other subjects.

The scientific exhibit on display throughout the Congress will consist of 250-300 booths showing advances in pediatrics and the field of medicine as a whole.

Following the Congress, three days will be spent in visits to hospitals in New York City. Delegates will then be taken on a post-Congress tour to other cities along the Atlantic Seaboard and perhaps in the Middle West. In each city a scientific program will be presented, including visits to pharmaceutical and food industrial plants.

## Elections

**The American Association of Petroleum Geologists** has elected as president Carroll E. Dobbin, regional geologist, U. S. Geological Survey, Denver, Colorado. Dr. Dobbin took office at the close of the 32nd annual meeting of the Association in Los Angeles, March 24-27.

**The Potomac Division of the American Phytopathological Society**, at its 4th annual meeting on February 20, elected V. F. Tapke, president; W. F. Jeffers, vice-president; W. W. Diehl, secretary-treasurer; and E. E. Clayton, councilor.

**The Southern Society for Clinical Research**, established to encourage research in the medical sciences, elected the following officers at its first annual

meeting in New Orleans, January 25: Tinsley R. Harrison, Dallas, Texas, president; William J. Darby, Jr., Nashville, Tennessee, vice-president; and Thomas Findley, New Orleans, Louisiana, secretary-treasurer. The following are councilors: Paul B. Beeson, Atlanta, Georgia; Robert M. Moore, Galveston, Texas; Joseph W. Beard, Durham, North Carolina; and Harold B. Greene, Winston-Salem, North Carolina. The founders' group consists of 40 men from various medical schools in the South, but membership is not limited to academic institutions.

**The Geological Society of Washington** elected the following officers for 1947: W. P. Woodring, U. S. Geological Survey, president; Ernst Cloos, Johns Hopkins University, and C. H. Dane, U. S. Geological Survey, vice-presidents; M. K. Carron, of the Survey, treasurer; M. H. Krieger and G. T. Faust, also of the Survey, secretaries.

## Recent Deaths

**V. M. Goldschmidt**, 59, director, Geological Museum, University of Oslo, Norway, died March 20. After several periods of imprisonment during the occupation of Norway, Dr. Goldschmidt escaped early in 1943 to Sweden and then to Scotland and England. He worked in the MacCauley Institute for Soil Research, Scotland, and Rothamstead Experimental Station in England during the remainder of the war.

**Samuel Morris**, a member of the chemistry staff of West Virginia University since 1916, died March 20 in Morgantown, West Virginia.

**The American Board of Pathology** has changed the dates of examinations to be given in 1947 to June 5-6 in Philadelphia and October 24-25 in Chicago. Applications for the Philadelphia examination will be received until May 1 and for that in Chicago until September 15. Inquiries should be sent to Robert A. Moore, American Board of Pathology, Washington University School of Medicine, St. Louis 10, Missouri.

**The National Registry of Rare Chemicals**, Armour Research Foundation, 35 West 33rd Street, Chicago, lists the following wanted chemicals: Trihexyl-

amine; trihydroxyglutaric acid; mercuric metatellurate; cupric metaborate; 1-methylanthracene; cobaltic sulfate; gallium metal and salts; lead tetraoxysulfate; laccase; polyphenol oxidase; thioveronal; 1-glyceraldehyde; 1-glyceric acid; erythritol and anhydride; dl-cysteine hydrochloride; tantalum pentachloride; columbium pentachloride; emetine; di-phenylhydroxylamine; and methylisopropylcyclopentanes.

**A New York State Science Council** will be provided under terms of a bill introduced in the state legislature by Thomas C. Desmond, state senator of Newburgh, New York, who said that "scientific changes, from splitting of the atom to supersonic airplane flight, demand that New York State plan wisely in a new Age of Science."

"Under the bill," he said, "the Governor, with the consent of the Senate, will appoint 20 members. Three need not be technical experts. The other 17 must be persons of 'outstanding qualifications and attainment,' one each from the following fields of scientific research: physics, chemistry, biology, botany, psychiatry, electrical engineering, sociology, agronomy, geology, zoology, anthropology, aeronautical engineering, bacteriology, surgery, medicine, civil engineering, and mechanical engineering.

"The Science Council will be empowered to: (1) make a continuous survey and study of modern developments in various phases of science and advise the Governor and legislature of such developments and their probable effect on the state generally and on social, commercial, and industrial institutions, health, power developments and other matters of state concern; (2) collect, analyze, and compile annually a list of scientific research projects contemplated by various state departments and agencies and advise such departments and agencies regarding the coordination, development, or restriction of such projects. This would result in a research priority list; and (3) develop a long range scientific research program for the state and encourage scientific research under public and private auspices.

"Members of the Council, who will receive no compensation except expenses, need not be residents of the state.

"Scientists, until recently, have been reluctant to get embroiled in the hurly-burly of shaping government decisions. Scientists must be encouraged to com-

out of the laboratories and to assume some responsibility for guiding public policies.

"Creation of this Science Council," Senator Desmond continued, "will give our state the benefit of the advice and judgment of some of the foremost scientists in the country. It will probably save our state from making unwise outlays of money for projects which may be outmoded a few years after construction by scientific developments."

### U. S. Civil Service Boards of Expert Examiners

Probably very few activities have been forced as serious reconversion tasks following the war as has the U. S. Civil Service Commission. The great upsurge of Federal employment occasioned by war necessities made necessary new techniques in recruiting, examining, hiring, and classification of employees. Most of these were temporary emergency measures. In the field of scientific personnel the break with the past was even more dramatic because of the unprecedented employment necessitated by the technical jobs to be done. The secrecy attending this type of work still further complicated the employment pattern.

The reconversion to a peacetime civil service pattern has, therefore, been more than usually difficult in the field of scientific personnel. An earlier issue of *Science* (April 12, 1946) has reported the establishment of the Advisory Committee on Scientific Personnel by the Civil Service Commission. This Committee has studied many problems relating to the status of scientists in Federal employment and has made a number of recommendations to the Civil Service Commission. As one of its recommendations, the Committee suggested the widespread extension of the plan of boards of expert examiners, used in some cases earlier by the Civil Service Commission. This program has been accordingly widely extended, particularly for scientific personnel. The Commission has set up regulations governing this new departure, and already a number of such committees are functioning.

Sixty-five such committees have been established in 18 departments and agencies, 6 of these being major departments and 12 being agencies. Of the 51 agencies in the departmental service, 29 are expected ultimately to set up committees.

The pattern is flexible, some agencies having central policy groups and subcommittees in the different branches. Others again have subcommittees as operating parts of a central operating committee. Other agencies have decentralized the work entirely into the hands of bureau or branch committees. Of the departments and agencies not yet having committees, several are expected to announce formations of committees shortly.

Already 22 examination announcements covering 168 examinations have been published by these committees. Examinations have already been held in 20 cases, and 6 registers of qualified candidates for Federal employment in the respective fields have been established. Eighteen other examination announcements are being currently prepared. These examinations cover subprofessional levels 4 to 8 (\$2,168-\$3,397), clerical, administrative, and fiscal series 5 through 15 (\$2,644-\$9,975), and professional series 1 to 8 (\$2,644-\$9,975).

These boards of expert examiners collaborate with the Civil Service Commission representatives in drafting recruiting standards, preparing examination announcements, constructing the examinations, developing schedules for rating experience and training, obtaining supplemental evidence from applicants as to their qualifications, rating examinations, etc. The members must be of outstanding competence in the scientific, professional, or technical fields in which the examinations are held.

The importance of the new system may be judged by the fact that it places responsibility for setting up examinations and all other steps involved in the selection of qualified candidates in the hands of operating scientists of mature experience with governmental laboratories and the particular branch of science. These men, together with representatives of the Civil Service Commission, who are expert in the legal phases of government employment and Commission regulations, supervise and carry out all of the necessary processes. They can initiate and carry out certain types of recruitment activities; and they can assist in disseminating factual information on government employment of scientific personnel.

The success of the plan will be largely dependent on the stature of the membership on committees. It is gratifying to note that the average grade level and professional standing of this membership

indicates a high degree of interest and devotion to the program. Taking half of the committees, including about 100 committee members, as an adequate sample, 96 are permanent civil service employees, the average length of service being 16 years; 33 have Doctor's degrees; 17 have Master's degrees; and 38 have the A.B. degree. In point of administrative responsibility, 11 are either heads or assistant heads of bureaus or agencies; 31 are division chiefs; 17 are assistant division chiefs; and 3 are section chiefs. The remaining 38 are professional employees. Almost half are of the grade P-7 or above. Two rank P-3; 12, P-4; 18, P-5; and 18, P-6. On the basis of these statistics it is clear that the committees are commanding the attention of many of the ablest and most experienced scientific employees.

Although it is too early to hazard an appraisal of the work of these committees or boards, it seems fair to expect that they will contribute greatly to the careful selection of scientists on the Federal payroll and hence contribute substantially to the ultimate soundness of government scientific work. They should also furnish an informal liaison, through the educational and scientific lay contacts of the members, to the scientific public for the interchange of authoritative information on personnel and on government employment in this field of work. This seems important in an age when the Federal role in science is clearly increasing in importance and must necessarily still further increase. (M. H. TRYTTEN, *Director, Office of Scientific Personnel, National Research Council.*)

### Make Plans for—

**The Electrochemical Society, Inc.,** annual congress, April 9-12, Louisville, Kentucky.

**American Chemical Society,** spring meeting, April 14-18, Atlantic City, New Jersey.

**Institute of Mathematical Statistics,** meeting on stochastic processes and noise, April 24-25, New York City.

**National Academy of Sciences,** annual meeting, April 28-30, Academy Building, Washington, D. C.

**American Medical Association,** centennial session, June 9-13, Atlantic City, New Jersey.

# COMMENTS

## by Readers

The announcement of the 6th International Congress of Experimental Cytology states: "The Congress will be open to scientists of all nationalities except German and Japanese."

To exclude from an international scientific congress any group of colleagues on the basis of nationality is to make a travesty of both appellations—international and scientific. Surely, science transcends considerations of nationality, as of race, color, and creed. For scientists to discriminate against colleagues on the basis of nationality is to commit the very crime against civilization which justified to many their participation in the war.

From the practical aspect no less than from the standpoint of scientific ethics is such a policy of exclusion disastrous. In science each builds on the other's work; exclusion is as harmful to those who practice it as to those excluded.

Sweden, host to the Congress, enjoys a deserved reputation for fairness and justice. I am convinced that the Swedish organization committee would welcome an expression of opinion on this policy. Other International Congresses are in preparation. If truly international, their influence can be great in restoring intellectual communication and mutual understanding. To that end, protests against exclusion of colleagues on such nonscientific grounds as nationality should reach the organization committees as soon as possible. (SALLY HUGHES-SCHRADER, Department of Zoology, Columbia University.)

Interesting calculations of the unequal distribution of diffusible non-electrolytes across a membrane have been made by C. L. Deasy (*Science*, October 25, p. 388); the inequality is a consequence of the presence of a nondiffusible non-electrolyte on one side of the membrane. Without questioning these calculations, one is inclined to be skeptical of the suggested importance of this phenomenon in the case of biological membranes.

No mention is made in Deasy's paper of the difference in pressure required to maintain equilibrium in an osmotic system of this sort. From the derivation given by F. T. Wall (*J. Amer. chem. Soc.*, 1944, 66, 446) it is clear that Deasy's equation is based on the assumption that this pressure difference exists, and that it is calculable from the mole fractions of solvent by the usual logarithmic equation. If the mole fraction of nondiffusible solute is 0.05, the distribution ratio for dissolved CO<sub>2</sub>, according to Deasy, is 0.89. It may be calculated, however, that the pressure difference at equilibrium must be, at 38° C., more than 70 atmospheres. The magnitude of this pressure indicates that the assumed conditions are hardly physiological. For a pressure difference of 25 mm. Hg, which is low enough to be physiologically possible, the distribution ratio becomes 0.99995. In the absence of very great differences in pressure, the calculated distribution will not be sufficiently unequal to require consideration in the explanation of physiological phenomena. (DAVID I. HITCHCOCK, Laboratory of Physiology, Yale University School of Medicine.)

May I add a footnote to Henry K. Beecher's interesting article on "Anesthesia's Second Power," appearing in *Science* for February 14, in the form of a quotation from Oliver Wendell Holmes that may help to throw the aforesaid "second power" into perspective?

"I once inhaled a pretty full dose of ether, with the determination to put on record, at the earliest moment of regaining consciousness, the thought I should find uppermost in my mind. The mighty music of the triumphal march into nothingness reverberated through my brain, and filled me with a sense of infinite possibilities, which made me an archangel for the moment. The veil of eternity was lifted. The one great truth which underlies all human experience and is the key to all the mysteries that philosophy has

sought in vain to solve, flashed upon me in a sudden revelation. Henceforth all was clear: a few words had lifted my intelligence to the level of the knowledge of the cherubim. As my natural condition returned, I remembered my resolution; and, staggering to my desk, I wrote, in ill-shaped, straggling characters, the all-embracing truth still glimmering in my consciousness. The words were these (children may smile; the wise will ponder): 'A strong smell of turpentine prevails throughout' (from *Mechanism in thought and morals*. Boston: Houghton Mifflin Company. Cf. also H. M. Johnson, "The real meaning of fatigue," *J. nat. Inst. industr. Psychol.*, 1929, 4, 433-45). (JOHN F. DASHIELL, Department of Psychology, University of North Carolina, Chapel Hill.)

The article by Haley and Flesher (*Science*, December 13, p. 567) suggests the following comment:

Besredka formulated the rule that if the same substance is injected into the same subject, in the same amount and in the same way, at intervals of 10 days, the resulting reactions will be approximately equal in intensity. If the interval is shorter, the intensity will be successively less and less; if the interval is longer than 10 days, the reactions will be successively more and more severe.

The authors state that the injection of a sensitizing dose increases the resistance of the animal to toxic injections of thiamine chloride. This is actually so in their experiment and due to the desensitizing interval of 7 days. Had the interval been more than 10 days, the effect of the sensitizing dose would have been the other way. An extensive experience with the rule makes me put considerable faith in it.

The case of death following injection of thiamine hydrochloride was reported by Webb and Reingold and quoted by the authors. The fatal injection was given after an interval longer than 10 days, and the previous injection had also been given after an interval of more than 10 days. This made the sensitization progressive. In both this case and the experiment of the authors, the responses occurred according to the rule.

It would be very interesting if the experiment were repeated with an interval of 14 or 21 days and the result reported. The rule is very important and not commonly observed. (JOSEPH F. BICAK, Moshulu Parkway South, New York City.)

## Cinephotomicroscopy of Normal Blood Circulation in the Cheek Pouch of the Hamster<sup>1</sup>

GEORGE P. FULTON and RUBY G. JACKSON  
Arthur D. Little, Inc., Cambridge, Massachusetts

BRENTON R. LUTZ  
Boston University

Precise microscopic studies of the peripheral circulation in the living animal require the use of thin, nonpigmented tissues which can be illuminated by transmitted light to reveal the structure of the walls of the smallest blood vessels. The number of suitable preparations is small, particularly in the mammal. Direct microscopic investigations in mammals have been made largely on the newly-formed blood vessels in transparent chambers inserted in the ear of the rabbit (2) and on the blood vessels in the mesentery of the gut (1). More recently, microscopic observations on the circulation in the wing of the bat have been reported (4). The investigators in this laboratory have used a new preparation for cinephotomicroscopic studies on small blood vessels, namely, the cheek pouch of the golden hamster (*Cricetus auratus*).

The hamster cheek pouch is a paired structure located inside the mouth cavity and used for temporary storage of food. *In situ* the wall of the pouch possesses numerous longitudinal folds which make it adaptable to considerable distention. The normal pouch is approximately 1½ inches in length and extends posteriorly to a position near the shoulder.

Its histological structure has been examined in sections stained with hematoxylin and eosin. The pouch is lined with stratified squamous epithelium consisting of from two to five layers of cells which become progressively flatter toward the surface, on which a slight amount of cornification is present. A relatively dense layer of fibrous connective tissue is found beneath the epithelium. Longitudinally arranged skeletal muscle fibers are numerous at the edge of this layer near the open end of the pouch but absent at the blind end. A layer of loose areolar connective tissue joins the wall of the pouch to the subcutaneous tissue of the cheek. Blood vessels are numerous in both connective tissue layers and skeletal muscle.

When the pouch is everted by gentle traction with forceps, the loose connective tissue between the subcutaneous tissue of the cheek and that of the pouch wall separates. The thin, nonmuscular portion of the pouch nearest the blind end is selected for use.

The animal is anesthetized with 6.5 per cent pentobarbital sodium (initial dose, .15 cc./animal, with fortification by .05 cc. increments at hourly intervals) and placed in a specially adapted Petri dish (6 inches in diameter). The dish is equipped

with a glass platform cemented to the bottom. The pouch is everted and the portion near the tip extended over the glass platform and pinned on paraffin, producing two flat layers. A crescent-shaped cut is made in the upper layer, forming a flap of pouch wall with the limbs of the crescent directed toward the free end of pouch. The flap is pulled back, exposing a portion of the inner or connective tissue aspect of the lower layer of the wall. A considerable amount of the loose connective tissue is removed by careful dissection under the binocular microscope. The pouch may be turned over and the inverted single-layered flap repinned with the epithelial aspect uppermost. The dish is fastened to the mechanical stage of a microscope equipped with a light-splitting prism for simultaneous viewing and motion-picture recording.

The effect of a substance in solution on a small blood vessel is studied by application with a micropipette to either the epithelial surface or the connective tissue side of the pouch.

Spontaneous intermittency of flow is very frequent in the small blood vessels of the hamster's cheek pouch. This is of two kinds: (1) that produced by the action of sphincters at the arterial end of capillaries; and (2) that produced by changes in the blood-pressure differential between the two ends of the capillary.

Intermittency of flow resulting from the action of smooth-muscle sphincters at capillary origins has been observed in the frog's retrolingual membrane (3). Similar sphincteric activity occurs in the small blood vessels of the hamster cheek pouch. A decrease in diameter of the capillary wall and deformation of red cells were observed at the point of branching of a capillary from the supplying precapillary arteriole, which did not change in caliber. This observation has been recorded in a motion-picture sequence taken at a magnification of 1,200 times. In the frog the arterioles, as well as capillary sphincters, may contract completely, stopping the flow of blood. In the hamster the arterioles rarely contract completely, and only small areas of tissue are deprived temporarily of a blood supply by the action of sphincters at capillary origins.

Intermittency of flow has been observed in capillaries when sphincteric action was not occurring in these vessels. In favorable preparations demonstrating this type of intermittency, the wall of the capillary remained completely open throughout the entire length. The flow stopped periodically in the capillary but continued without observable change in either the arteriole or the venule. Actual reversals in direction of flow in capillaries have been observed frequently. Intermittency of this type may be explained on the basis of changes in the blood-pressure differential between the two ends of the capillary involved.

Both types of intermittency, that involving sphincteric activity of the capillary origin and that without, have been observed in adjacent small blood vessels in the same vascular area. It is possible that pressure changes producing the in-

<sup>1</sup> This research work was supported by Bristol-Myers Company, New York.

termittency may be caused by small changes in caliber of the arterioles or by sphincteric activity in an anastomosing portion of the vascular bed.

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## Vascular Changes in the Wings of Bats

RAYMOND B. COWLES

*Department of Zoology, University of California, Los Angeles*

In a series of articles published since 1939 it has been proposed that acquisition of progressively higher operating temperatures may have been one of the fundamental factors in the evolutionary processes of terrestrial animals (2, 4, 5). It has also been suggested that transgression of the threshold of either somatically or germinally tolerable temperatures, particularly the latter, constitutes one of the major hazards to survival (3, 4, 5, 7) and even may be the key to extinction in some of the major groups of terrestrial animals (2; for contrasting views, see 1). In these papers it has also been stated by the present writer that the existence of heat sensitivity in male germinal processes, in combination with the thermal progression seeming to characterize major groups of terrestrial animals, may have expedited the process of evolution on land.

Thinking along this line inevitably points to the importance of investigating all instances in which there is an appearance of testicular thermal tolerance equal to that of the somatic cells.

Among terrestrial animals, the exceptionally high normal body temperatures of the birds, especially when considered in conjunction with the internal location of their testes, would seem to indicate that they would fit this category since their spermatogenic activity must take place at abnormally high temperatures. However, until additional observations have been made, this will remain only a partially acceptable assumption. The universality of heat susceptibility in other groups and Riley's findings on interrupted spermatogenesis (9) suggest the possibility that temperature may influence spermatogenesis in the English sparrow, and this view is strengthened through the finding by Cowles and Nordstrom (8) of an avian analogue to the mammalian phenomenon of testicular descent and possible scrotal thermoregulation. In this avian phenomenon it was demonstrated that the testes of Brewer's blackbird migrate a short distance, so that, while they are spermatogenetically active, they lie between two folds of the abdominal air sac.

Following the same lines of thought that led to investigations on the air sac-testes relationship in birds, it became apparent that a somewhat similar situation might be encountered in some Nearctic bats.

Several species of temperate-zone bats are known to breed in late summer or early fall, and throughout the summer months many of them are daytime occupants of hot attics; yet, despite this exposure to theoretically unfavorable temperatures, they are among the minority of nonscrotal vertebrate animals which reach the peak of spermatogenic activity toward the end, rather than before, the season of maximum summer tempera-

tures. This situation is in marked contrast to conditions found in other terrestrial organisms, since the great majority of birds, most nonscrotal mammals, reptiles, and amphibians give at least the appearance of requiring a prolonged period of cool or cold winter weather prior to resumption of spermatogenesis. This condition (winter rest?) strongly suggests that there is need of moderate thermal conditions for testicular rehabilitation from heat effects. It seems possible that our long, hot summers may explain the widespread regression of the testes characterizing so many temperate-zone animals, a condition that frequently sets in not long after the onset of hot summer weather. Certainly there is a strong resemblance between this situation and that produced in *Xantusia vigilis* by artificial heat sterilization (7), and a similar condition is illustrated by the 13-lined ground squirrel (10).

Because of the effectiveness of their thermoregulatory device, scrotal mammals seem not to be so rigorously limited to early spring or summer breeding. Although exceptions to this general rule of postwinter breeding are known, they are not numerous. However, because of the known effects of light on gonadal activities it will be necessary to test the respective missions of these two factors.

Although Nearctic bats are hemipokilothermic organisms, they are characterized by testicular descent and testes migration into the tail membrane, the uropatagium, where cooler conditions should prevail. In spite of this presumable protection, it is possible that this effect might be canceled by two heating factors: (1) the nature of their daytime retreats, which might prevent the normal daytime fall in temperature; and (2) their heat-generating nocturnal activities, chiefly the pursuit of food, which is to a large extent captured while in flight. The importance of this latter factor is accentuated by the bat's notable capacity for heat generation, a requisite for these animals to enable them to preheat their bodies in preparation for flight. Taken together, these two conditions suggest that the bats may either furnish an example of an animal that has succeeded in achieving identical somatic and spermatogenic heat tolerance or that they have some unusually effective means for heat dissipation and thermal regulation.

For a preliminary excursion into the thermal relationships of these animals it was clear that the effectiveness of the flight membranes should be evaluated as heat-dissipating and thermoregulatory structures. These comparatively large areas are usually devoid of hair and are highly vascularized and thus suitable for heat exchange mechanisms. A preliminary rough survey of ratios between the surface areas of the furred body and the naked flight membranes shows that these proportions range from 4:1 to as much as 8:1 in Nearctic bats but 12:1 in the tropical fruit bats.

In the common and rather typical bat, *Myotis yumanensis sociabilis*,<sup>1</sup> a superficial observation on the degree of vascular change in the network of blood vessels in the flight membranes clearly revealed marked changes in the amount of blood passing through these tissues. These changes were readily correlated with body temperatures.

In experiments conducted up to the present time it has been found that engorgement of the vascular plexus in the membranes is induced by elevating the body temperature to be-

<sup>1</sup> For the identity of this bat and for information on the position of the testes in the uropatagium I am indebted to Mr. Kenneth Stager, of the Los Angeles Museum.

tween 40 and 41° C., but that between 10 and 38° C. there are no gross, readily perceptible alterations in the amount of blood flow. Throughout this range the wing and tail membranes retain the comparative pallor characteristic of low-temperature conditions. When the change does occur, it is so sudden and so notable that students readily perceive the difference even at a distance of several feet. Exact measurements of temperature differences between the arterial and venous flow are expected to reveal even more interesting information.

That bats might possess somatic and spermatogenic thermal homogeneity seemed as reasonable as to have supposed that the birds might do so; however, the morphological arrangements in both of these animals seem to point to a provision for heat protection, and it is now reasonable to proceed to the acquisition of more exact physiological data, with the expectation that lower testicular temperatures can be demonstrated during the period of spermatogenesis.

If neither of these animals can be shown to possess somatic and spermatogenic thermal equality, the condition should still be sought in other organisms. However, if it is demonstrated that this thermal difference is universal, as our present limited information suggests it may be, it seems probable that some profound and fundamental difference will be found in the basic physical or chemical attributes of these two classes of cells.

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## Carbon and Hydrogen in Rubber Hydrocarbon

HENRY J. WING

16 Grandview Avenue, Stamford, Connecticut

Analyses, by combustion, of rubber hydrocarbon separated from rubber latex and crystallized from ethereal solutions at low temperatures yielded combined percentages of carbon and hydrogen which totaled slightly less than 100 (4). Midgley (1) assumed the difference to be due to oxygen, and he and his co-workers have used the results to substantiate their argument that natural rubber is not a true hydrocarbon but contains a small amount of oxygen in chemical combination.

Later, Roberts (2) reported that he had isolated the portion of rubber which contained oxygen. This he called caoutchol, to distinguish it from the hydrocarbon, which he named caoutchene. He used Midgley's results to confirm his findings, which he attempted to apply in a new way to the familiar two-phase theory of Fessenden as an explanation of the

properties of rubber. However, Schidrowitz (3) has indicated that the method used by Roberts to separate the caoutchol is not free from possible criticism. Some steps in the procedure, e.g. milling, promote oxidation.

Since publication of the analyses made at the Bureau of Standards the values for the atomic weights of carbon and hydrogen have been changed from 12.00 and 1.0078 to 12.010 and 1.0080, respectively. When these earlier results are recalculated with the new atomic weights, the sums of carbon

TABLE 1  
COMPOSITION OF RUBBER (RECALCULATED)

	Hydrogen	Carbon	Sum	Ratio Hydrogen: Carbon
Rubber hydrocarbon uncrystallized	11.85	88.03	99.88	0.1346
	11.84	88.11	99.95	.1343
	11.77	87.66	99.43	.1342
	11.85	88.03	99.88	.1346
	11.82	87.92	99.74	.1344
Average			99.78	
Crystallized once	11.86	88.06	99.92	.1346
	11.82	88.02	99.84	.1343
Average			99.89	
Crystallized three times	11.87	88.31	100.18	.1344
	11.86	88.13	99.99	.1345
Average			100.05	
General average			99.87	

and hydrogen are increased by 0.061 per cent. When the results reported in the earlier paper are corrected for two typographical errors and this increment is added, the recalculations are as shown in Table 1.

Several things should be said about these results if they are to be used as a basis for judging whether oxygen constitutes a part of the normal rubber molecule: (1) The sum of carbon and hydrogen found increased with increasing purification of the rubber. (2) The most carefully purified material gave an average sum of carbon and hydrogen in excess of 100 per cent, and the four analyses of hydrocarbon which had been recrystallized at least once averaged 99.97. (3) The differences between analyses of the same material were greater than the average difference between the sum of hydrogen and carbon and 100 per cent. The latter cannot, therefore, be regarded as certainly significant. (4) The absolute purification of the rubber hydrocarbon cannot be assumed. Substantially all probable impurities, including water, ether, dissolved or adsorbed gases, inorganic material, and products of oxidation of the rubber itself, would have lowered the sums of hydrogen and carbon observed.

Certainly the results leave very little, if any, of the weight of the rubber to be accounted for as normally combined oxygen. This is not all, however. The observed ratio of hydrogen to carbon is higher than the theoretical (0.1343) by an amount that appears less significant than it really is, in comparison with the total weight of carbon and hydrogen, because of the small weight of hydrogen. For the entire

series of analyses the weight of carbon dioxide found was 0.21 per cent lower than that computed from the weight of rubber burned, the weight of the water being only 0.06 per cent low. For the four samples of recrystallized rubber, the carbon dioxide was 0.09 per cent low and the water 0.08 per cent high. These differences are in the direction we would expect if the discrepancy in the total weight were the result of probable impurities in the rubber, particularly water and ether; on the other hand, the presence of oxygen combined as hydroxyl would not affect the ratio of hydrogen to carbon, and in the form of other probable radicals it would reduce that ratio.

If the small difference between the theoretical value and the sum of hydrogen and carbon is to be considered significant, the difference between their theoretical and observed ratios must also be significant, and this definitely indicates incomplete purification rather than combined oxygen, as postulated by Midgley.

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## Variation Among Lamb Carcasses in the B Vitamin Content of Meat<sup>1</sup>

SYLVIA COVER, ESTHER M. DILSAVER, and RENE M. HAYS

*Agricultural and Mechanical College of Texas,  
College Station*

It is generally accepted that ruminants do not require the B vitamins. Hence, the variation in ration content may be assumed to have no effect on the B vitamin content of their meat.

Nevertheless, considerable difference in B vitamin content of the raw meat of different carcasses of beef has been reported (1). This difference has been questioned on the grounds that there was no way to remove the variation associated with carcasses from that associated with performing the analyses at different times. In more recent experiments with groups of lamb carcasses, however, there have been findings similar to those in the previous study. The additional evidence, moreover, was obtained from an experimental design improved to meet the previously mentioned criticism.

The experiment was originally planned to overcome as nearly as possible the suspected variation between carcasses. But the variation was notable even under these conditions. Because the details of the entire experiment of which this study is a part will be given in subsequent papers, only those details concerned with carcass differences will be given here.

The samples of meat were obtained as follows: Cubes of meat from a wholesale cut (triangle) were mixed for each of four carcasses separately. Enough cubes to weigh exactly 125 grams were taken from each of the four carcasses and combined to make one 500-gram sample. Equal numbers of 500-gram packages were placed in each of two flat pans and frozen in the deep freezer,

<sup>1</sup> The work on which this paper was based was supported in part by a grant from the National Live Stock and Meat Board.

where they were kept until needed. To obtain replications, this entire procedure was repeated with meat from other lots. Six replications were employed, making a total of 24 lamb carcasses. Storage periods between killing and freezing were held constant, as were those between freezing and analysis, so that these storage periods would not be a possible cause of variation in vitamin content. The same sample was used for the determination of the following B vitamins: thiamine, pantothenic acid, niacin, and riboflavin.

In preparation for testing, one of the two pans in a replicate was removed to the laboratory, where the samples were allowed to thaw in the refrigerator. Two of the samples were analyzed raw, the other samples after cooking. One week later the other

TABLE 1  
VARIATION IN VITAMIN CONTENT BETWEEN REPLICATES  
(GROUPS OF CARCASSES)

Replicate No.	No. of samples	Thiamine	Panto- thenic acid	Niacin	Ribo- flavin
		Actual content (μg./gram dry free-fat basis)			
1	4	8.22	24.75	262.9	12.91
2	4	9.33	25.49	257.4	11.58
3	4	11.72	25.16	231.9	11.37
4	4	7.01	28.65	269.8	10.57
5	4	8.34	24.30	287.2	10.40
6	4	8.15	26.73	270.5	11.57
Greatest difference (highest —lowest).....		4.71	4.35	55.3	2.51
Percentage difference*.....		67	18	24	24
F value of replicates†.....		28.29‡	13.80‡	25.13‡	37.78‡

\* Calculation =  $\frac{\text{greatest difference} \times 100}{\text{lowest replicate}}$

† Calculated from dry fat-free basis.

‡ Error terms were remainder after replicates, order, and O × R were removed.

F values needed for significance were: 0.05 level = 3.11, 0.01 level = 5.06.

pan of samples from the same replicate was removed and the raw samples treated in like manner. Thus, two combinations of the data on raw meat were possible: those associated with order of analysis and those associated with replications. Since the data were collected in this fashion, the variation associated with doing the analyses at different times could be removed from replications by an analysis of variance.

The average vitamin content of each of the 6 replicates is given in Table 1. The variation is shown by the differences between the highest and lowest value, the percentage difference, and the F value. As will be seen, the difference between replicates is highly significant for all of the four vitamins in lamb. The percentage difference in each case is above any recognized value for experimental error. It would appear that the highly significant difference between replicates is associated with something other than the different occasions on which the analyses were made. Carcasses (or groups of carcasses) are apparently the dominant factor associated with replicates. It seems probable that the difference would have been even greater had the analyses been made on individual rather than on groups of carcasses.

That the meat of lamb varies in B vitamin content from carcass to carcass is of unusual interest because lambs are known not to require the B vitamins. Sheep have been shown to synthesize thiamine, pantothenic acid, and riboflavin in the rumen (2), and an excretion study indicates that they also synthesize niacin (3).

There are no clues as to why some of the animals had higher B content in the meat than others, because production histories could not be obtained during the emergency period when this meat was purchased. Whether the factors which control the B vitamin deposition in the meat are environmental or genetic must be determined by further research.

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## The Effects of Cytochrome C in Anoxia

I. HERBERT SCHEINBERG and H. O. MICHEL

*Biochemistry Section, Medical Division,  
Chemical Corps, Edgewood Arsenal, Maryland*

Proger and his co-workers (4) have reported that intravenously administered cytochrome C is capable of mitigating the physiological effects of anoxia. In view of these reports it was thought that cytochrome C might be of value in preventing cyanide intoxication. Experiments to be reported elsewhere failed to demonstrate any significant effect of cytochrome C in cyanide-poisoned rats. Further work was then carried out in an attempt to confirm two findings of Proger and his group which were susceptible to objective and quantitative measurement: the effects of cytochrome C on the organ content of easily hydrolyzable phosphorus compounds, and the survival times of anoxic rats.

The resynthesis of adenosine tri- and diphosphate from adenylic acid and inorganic phosphate is coupled to oxidative processes (3) and should be diminished under conditions of anoxia. The tissue content of adenosine tri- and diphosphate parallels the content of easily hydrolyzable phosphorus (2, 3). In addition, under conditions of anoxia the blood level of lactic acid increases (1). In our experiments the amount of easily hydrolyzable phosphorus in heart and kidney, the blood level of lactic acid, and the measurement of survival times were used to quantitate the effect of anoxia on rats and to measure the value, if any, which cytochrome had in the treatment of anoxia.

In the first experiment both members of pairs of littermate white rats were given 2.0 cc./kg. of physiological saline intravenously. One member was then placed in an atmosphere of 3.9 per cent oxygen, and the other allowed to breathe air. After 8 minutes determinations of the easily hydrolyzable phosphorus ("7-minute phosphorus") of kidney and heart and of the blood lactic acid were made. These revealed a significant difference in all three quantities between those rats which breathed 3.9 per cent oxygen and those which breathed air (Experiment 1, Table 1).

In the second experiment both members of pairs of littermate white rats were placed in an atmosphere of 3.9 per cent oxygen after one had been given approximately 20 mg./kg. of cytochrome C in saline intravenously and the other an equal volume of physiological saline. Determinations of the same

TABLE 1  
EFFECT OF CYTOCHROME C ON SEVERAL MANIFESTATIONS OF ANOXIA IN RATS

Experiment	No. of pairs	Treatment of animals	Mean of differences between test and control*	P*
1	7	Pairs of rats (test and control) pretreated with saline. Test placed in an atmosphere of 3.9 per cent oxygen for 8 minutes; control remained in air.		
		Kidney 7-minute phosphorus (mg./100 grams fresh tissue)	-2.37	0.025
		Heart 7-minute phosphorus (mg./100 grams fresh tissue)	-5.07	0.025
		Blood lactic acid (mg./100 cc. blood)	110.8	Less than 0.01
2	11	Pairs of rats (test and control) placed in 3.9 per cent oxygen for 8 minutes. Test pretreated with cytochrome C; control pretreated with saline.		
		Kidney 7-minute phosphorus (mg./100 grams fresh tissue)	0.27	0.68
		Heart 7-minute phosphorus (mg./100 grams fresh tissue)	-0.78	0.41
		Blood lactic acid (mg./100 cc. blood)	-0.64	More than 0.90
3	25	Pairs of rats (test and control) placed in 2.8 per cent oxygen. Test pretreated with cytochrome C; control pretreated with saline.		
		Survival time (min.)	0.66	0.45

\* The differences between the test and control animals with respect to the measured quantities were found, and from these the values of P, representing the probabilities that the observed differences were due to chance, were determined.

three quantities as in Experiment 1 revealed no significant difference between the cytochrome C and saline pretreated animals (Experiment 2, Table 1).

In the third experiment both members of pairs of white rats of the same age, weight, and sex were placed in an atmosphere of 2.8 per cent oxygen after one had been given 5 mg. of cytochrome C in saline and the other an equal volume of physiological saline intravenously. There was no significant difference

in the survival times of the members of each pair (Experiment 3, Table 1).

These results do not confirm the findings of Proger and his collaborators in similar experiments.

The experiments will be reported in detail elsewhere.

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## Effects of Ultraviolet Radiation on Visual Thresholds

ERNST WOLF

*Biological Laboratories, Harvard University*

In a recent paper (1) E. Ludvigh and V. E. Kinsey demonstrated that visual threshold light-difference sensitivity and critical flicker frequency tests in the fovea are not affected by previous exposure for 5 minutes to the radiation of a 1,000-watt mercury vapor arc, from which most of the visible and almost all of the ultraviolet radiation shorter than 320  $m\mu$  were filtered out. These findings seem to contradict the results obtained with baby chicks (2, 3), in which extensive changes in sensitivity thresholds were obtained and which the authors cited can attribute only to the marked difference in absorption and in general physiological characteristics between the eyes of baby chicks and those of adult human beings. They conclude that ultraviolet radiations longer than 320  $m\mu$  encountered in nature are without deleterious effect on these functions of the normal human eye.

For the chick (2, 3) as well as for the human eye (4) it has been shown that pre-exposure to the radiation of a mercury vapor arc emitting ultraviolet light above 285  $m\mu$  in addition to the visible wave range raises the final dark-adapted thresholds considerably above the normal level (1.3 log unit for the chick and 0.25 log unit for the human eye), as compared with pre-exposures to the same source but with all ultraviolet filtered out. The adapting brightness is in both cases the same, and hence it is assumed that the final threshold differences are due to the ultraviolet. In Fig. 1 data are given for one human observer (light exposure, 10 minutes, with a large adapting field; test with a 12.5° square field; central fixation; presentation, 1/25 second) and for a series of baby chicks (pre-exposure, also 10 minutes). The data for the human eye are individual readings; the chicken data are averages. The figure shows the interesting fact that in both cases the cone part of the duplex dark-adaptation curves is unaffected by the pre-exposure to ultraviolet, while the rod segments are clearly altered. For the human curve the onset of rod adaptation is delayed for about two minutes, the cone segment overshooting the normal beginning of rod adaptation and remaining above the previously established level until termi-

nation of the test. For the chick the slopes of cone and rod segments are quite different from those for the human, so that, due to the steepness of the cone segment, an overshooting is not apparent. It is also found that a reduction of the extent of the ultraviolet spectrum reduces the effect on final thresholds; light containing only wave lengths above 365  $m\mu$  has no effect. Ultraviolet alone, after largely eliminating visible light, acts in qualitatively the same manner as visible light to which ultraviolet has been added.

Previously it has been pointed out (3, 4) that the effect of ultraviolet upon the cones is probably prevented by their

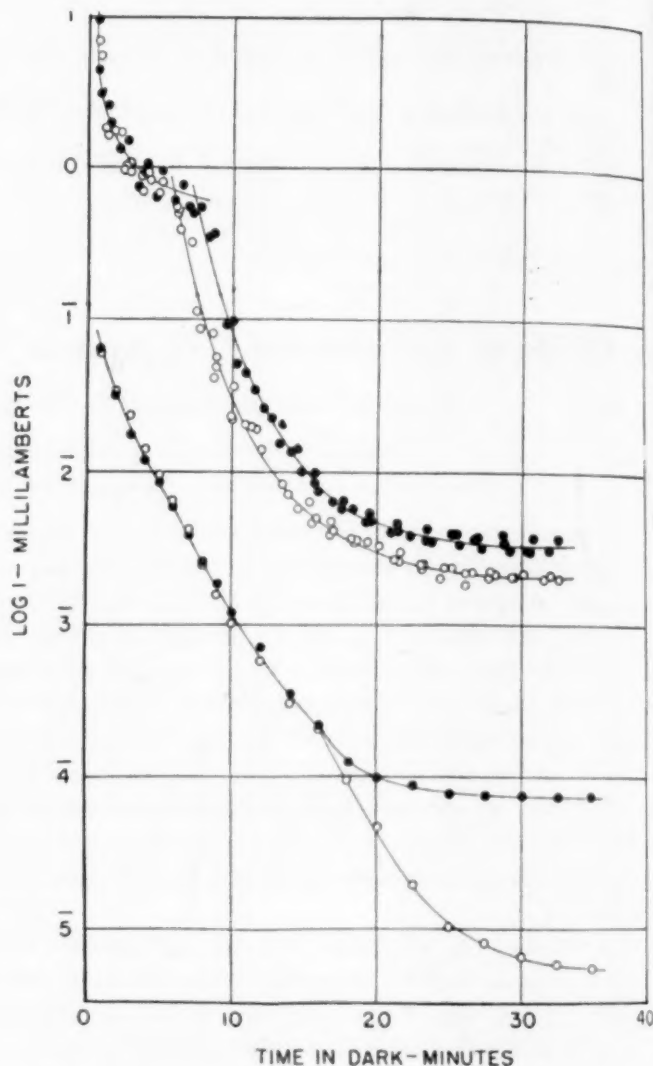


FIG. 1. The course of dark adaptation of human eye (above) and for baby chicks (below) after exposure to the radiation of mercury vapor lamps. Open circles indicate that the ultraviolet has been filtered out; black circles, that ultraviolet above 285  $m\mu$  is present.

dense pigmentation, while it acts upon the pigment-free rods. Therefore, while testing foveal intensity discrimination, or flicker thresholds, after pre-exposure to ultraviolet, it is obvious that an effect upon visual thresholds cannot be expected, since one is dealing with an irresponsive pure cone population of sensory units with exclusion of the rods. A test of this kind has no relevance to the problem of the presence of an ultraviolet effect upon the peripheral rod units.

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# IN THE LABORATORY

## Determination of World Plant Formations from Simple Climatic Data

L. R. HOLDRIDGE

Department of Botany,  
University of Michigan, Ann Arbor

While attempting to understand relationships between the mountain vegetation of an area in Haiti and other vegetation units of the island and surrounding regions, the literature was searched unsuccessfully for a comprehensive system which presented formations or vegetation units on a relatively equal or comparable basis. To fulfill such a need, a chart (Fig. 1) was

and the lower montane belt, a frost line is recognized which separates the low subtropical region and the subtropical belt formations as vegetation units usually present between the 24° isotherm and the limits of killing frosts.

The precipitation value used for a locality is the average mean annual precipitation in millimeters. The temperature and precipitation values for any site plotted logarithmically on the chart determine a point which falls within a hexagon representing a formation. When the point falls within one of the border triangles of a hexagon, the vegetation of that area will show a transitional character.

For altitudinal adjustment, approximate elevation in meters above sea level must be known to be certain of the region to

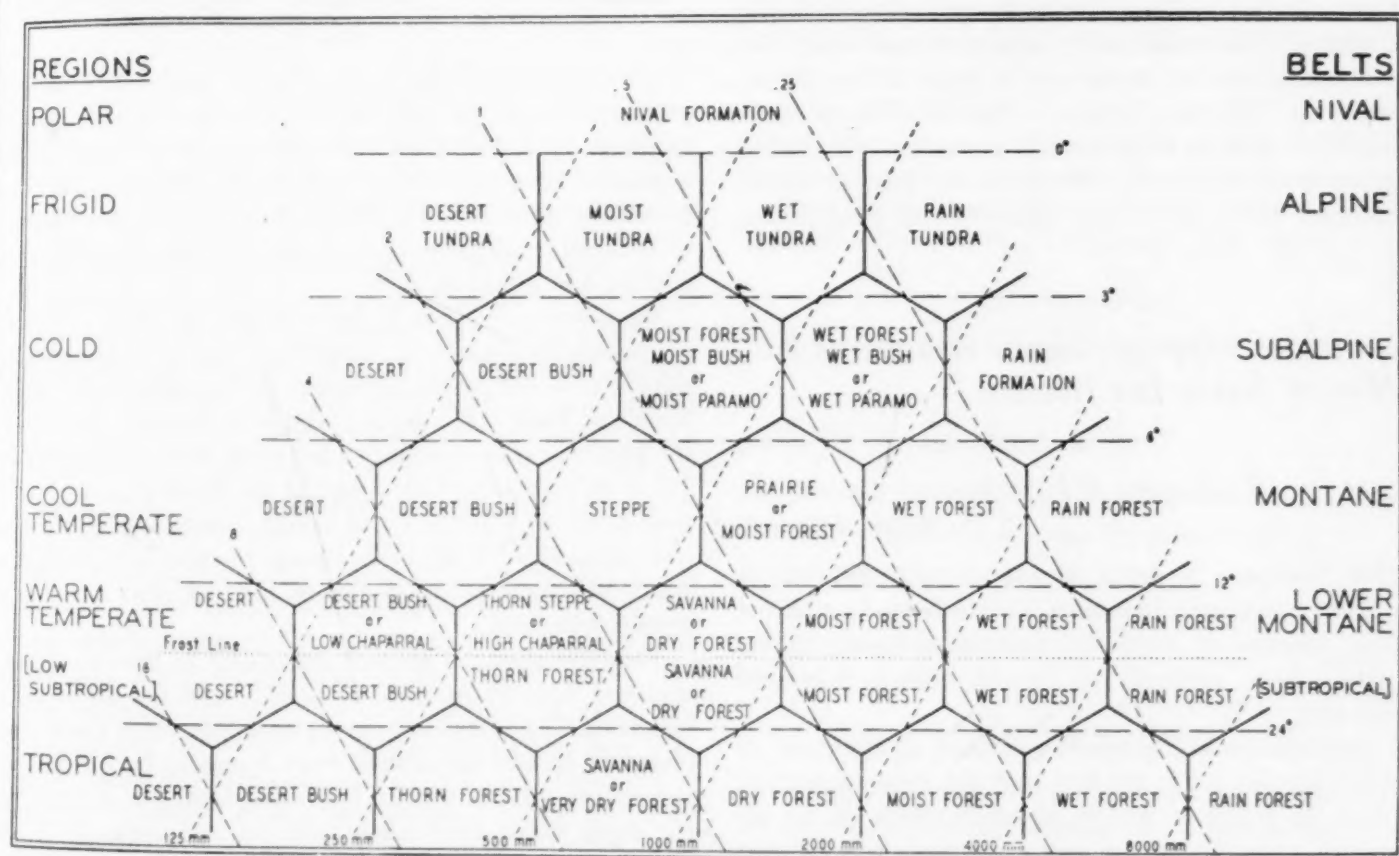


FIG. 1

constructed which differentiates the vegetation of dry land areas of the world into 100 closely equivalent formations separated by temperature, precipitation, and evaporation lines of equal value.

Mean temperature values used approximate those of the growing season and are determined for specific sites by adding the average mean monthly temperatures greater than 0°C. and dividing by 12. Such values for lower elevations establish several regions north and south of the heat equator, as indicated on the left, and at higher elevations the belts listed at the right. Because of the difference in vegetation caused by the presence or absence of frost in the warm temperate region

which the formation belongs. All altitudinal belts will be found only in the tropics. In other regions, only the belts above the basal formations of the region on the chart will be encountered. Elevations of formation boundaries vary considerably, but the ranges of the belts approximate the following: nival— indefinite, alpine—500 m., subalpine—500 m., montane— 1,000 m., and lower montane alone or with the subtropical if present—2,000 m. The tropical basal region varies from 0 to 1,000 m.; the warm temperate alone or with the low subtropical, 0–2,000 m.; and the basal formations of the other regions, from 0 m. to the maximum for the corresponding belt.

Thus, a station below 500 m. in elevation with means of

8°C. and 360 mm. would fall in the cool temperate steppe formation. If the same values were obtained for a station 2,500 m. above sea level, the formation would be warm temperate montane steppe. Formations with common precipitation and temperature boundaries, but occurring at different elevations in adjacent regions, are termed linked formations because they show closer affinities than other adjacent formations separated by temperature or precipitation boundaries.

The evaporation lines are not essential to the use of the chart. These are inserted to show the other balancing factor in the chart, and the values indicated are thought to represent the number of times the actual precipitation could be evaporated in one year at sea-level atmospheric pressure. No data are available to support these suggestions regarding evaporation.

The chart is designed to make broad divisions and to show actual relations between climatic vegetation formations. Local edaphic conditions, such as salinity or a high water table as well as alteration by man, can obviously change the appearance of the vegetation to a great extent. Two or more names were found necessary at times, partly because formations from both low and high elevations are represented on a two-dimensional chart and partly because certain easily determined factors, such as topography in grass or tree formations and the difference between continental- and mediterranean-type climates, make possible vegetations of a distinct appearance under similar climatic conditions. Further details and examples will be given in a paper now in preparation.

## Detection of Hypoglycemic Reactions in the Mouse Assay for Insulin

D. M. YOUNG and A. H. LEWIS

*Connaught Medical Research Laboratories,  
University of Toronto*

In 1946 Thompson (4) described a sloping-screen technique for use in the mouse assay of insulin. This technique avoids the subjective selection of convulsive animals necessary in the more conventional methods (2, 5) and reduces personnel requirements.

One disadvantage of Thompson's method, as observed in these Laboratories, lies in the fact that the mice do not fall away from the screen until signs of insulin shock are far advanced, and, even though the mice are immediately injected with glucose, the mortality is high.

Fig. 1 shows a unit which was developed in these Laboratories in an attempt to overcome the difficulty noted.<sup>1</sup> The unit consists of 6 hollow cylinders, 8 inches in diameter and 27 inches long, mounted at an angle of 60° on wooden rollers. Five inches of each end of each cylinder is constructed of 22-gauge galvanized iron, and the central section, 17 inches in length, is constructed from ¼-inch wire mesh. The wooden rollers, motor driven at a constant speed, make contact with the cylinders through plywood bands which encircle the cylinders 2½ inches from top and base. Each cylinder rotates once every 40 seconds. The cylinders may be removed from the

rollers for cleaning and emptying. The unit is housed in a room with a temperature range of 23–25° C.

In performing an insulin assay, mice are injected subcutaneously with suitable amounts of the insulin preparations to be compared and are loaded into the rotating cylinders, each of which will readily accommodate 40 animals. The rotation assures that the foothold of the mice is never secure for long. At the first sign of insulin shock they fall away into trays placed beneath the individual cylinders. These contain rabbit chow pellets, and in almost all cases the mice falling into the



FIG. 1

trays are able to eat sufficient food to relieve their hypoglycemic signs, so that injection with glucose is unnecessary. When a specified interval has elapsed after injection, the mice which have fallen away from the cylinders are counted, the numbers so obtained being used in computing the required estimates of potency and precision.

Results obtained from 35 consecutive assays were utilized in estimating the slope of the logarithm-dosage response relationship. A two-dose technique similar to that outlined by Miller, Bliss, and Braun (3) was employed in each assay. The ratio of the higher dose of standard to the lower dose of standard was 2:1 in all cases. The higher dose in the different assays varied from 0.025 to 0.010 I. U. of insulin/mouse. Thirty-six mice were used at each level. In each assay the numbers of reactions which had occurred at 45 and 60 minutes after injection of insulin were noted.

The percentages of animals responding to the two doses of standard were transformed to probits, and the slopes of the logarithm-dosage response curves were computed. The average slopes at 45 and 60 minutes were found to be 3.2 and 3.3, respectively. There was no indication from the  $\chi^2$  tests that the slopes varied significantly from one assay to another. The values obtained are of the same order of magnitude as the value 3.5 obtained by Marks and Pak (2) and the value 3.0 obtained by Trevan as calculated by Irwin (1).

The mortality among the first 18,000 mice placed on test was found to be 1.7 per cent, an appreciable decrease from mortalities of 7–10 per cent experienced in these Laboratories with more conventional procedures. It was found that two operators, using the unit described, could perform all the work necessary for a 1,000-mouse assay in one working day, whereas with the procedure previously used four operators were employed to perform assays of this size. Efficiency was increased somewhat by assaying two unknown samples of insulin (two cylinders per unknown) against one standard (two cylinders) on each run.

It is reasonable to suppose that the apparatus might also

<sup>1</sup> The authors wish to express appreciation to W. Parkinson and D. P. Joel for technical assistance in construction of the apparatus.

be employed to assay compounds counteracting the action of insulin (cortical and pituitary hormones), central nervous system depressants (anesthetics and hypnotics), and compounds affecting neuromuscular transmission (curare), as well as in studies relating to the development of tolerance to certain drugs.

In assaying drug samples of unknown origin by means of the apparatus described, special attention will have to be paid to the qualitative relationship between unknown and standard material. The results of an assay will be misleading if the mice react to some agent in the unknown preparation other than the specific substance under study.

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## Apparatus for Mustard Gas Treatment<sup>1</sup>

J. G. CARR

*Institute of Animal Genetics, University of Edinburgh*

The early work which led to the discovery that mustard gas could induce mutations in *Drosophila melanogaster* as efficiently as X-rays was carried out by pumping mustard gas dissolved in cyclohexane at intervals into air flowing past the flies (1). This method was rather unsatisfactory, as apparently similar treatments gave widely discordant results, and a few accidents occurred among those handling the mustard gas. The new apparatus to be described has several advantages over the old: (1) Dosage is controlled and repeatable; (2) a single charge of mustard gas lasts for many experiments; (3) contact with mustard gas is avoided except during recharging; (4) another substance in addition to mustard gas is not used; and (5) the apparatus is ready for use at any time.

The following train attached to an aspirator is set up in a fume cupboard: air intake with cotton-wool filter; tap; bubbling device (two potash bulbs) containing pure mustard gas; three-way tap; trap; *Drosophila* vial; trap; wash-bottles containing HNO<sub>3</sub>. The aspirator consists of two winchester quarts fitted in series in the usual way. Rubber connections are employed throughout.

The insects are exposed by placing them in a clean, empty vial in the apparatus and turning the three-way tap to admit air. When the rate of flow of air through the wash-bottles has been adjusted (about 3 bubbles/second), the taps are turned to admit the air via the mustard gas. This air is saturated with mustard gas vapor, and the amount depends (but only slightly) on the temperature. Using Florida-4, an inbred stock, at a temperature of approximately 10° C., the flies show some discomfort after about 8 minutes, after 20 minutes do not often travel the entire height of the vial, and after 30 minutes a few

remain motionless on the bottom of the vial. At the close of the run, the two-way tap is shut, and the three-way tap adjusted to admit air. A period of about 10 minutes is allowed to wash away all traces of mustard gas. The flies rapidly recover when the mustard gas is no longer admitted. During the run, the operation of the wash-bottles and bubblers causes the air flow to surge; this is regarded as an advantage, as it ensures thorough mixing of the air in the exposure chamber.

If a large number of flies is used, the vial becomes very moist, because the flies excrete much fluid when the mustard gas reaches them. If a piece of coarse filter paper is placed in the vial, most flies rest upon this, and the moisture is absorbed and evaporates more easily in the air stream.

As originally designed, the concentration of mustard gas in the air stream could be raised by heating the bulbs and thus increasing the vapor pressure of the mustard gas. To prevent subsequent condensation, the first trap and fly vial must then be raised to the same or a greater temperature. No need was found for this arrangement, however, and all dosage work has been performed by varying the time of exposure.

Of course, this arrangement controls only the external concentration of mustard gas. The amount which reaches the nucleus of any organ will vary, due to differences of chemical composition of the organ and consequent solubility of mustard gas. Though constant for similar organisms, the apparatus cannot, like X-ray machines, deliver an equal dose to the nucleus of all nuclei of any species exposed in the same way.

With this apparatus, Florida-4 males exposed for 15 minutes show about 5 per cent sex-linked mutations, using the CIB test.

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## Acetone-desiccated Adult Tissues as a Source of Cell Growth-promoting Extracts

E. MARGOLIASH

*Department of Experimental Pathology,  
The Hebrew University, Jerusalem, Palestine*

During the course of our studies on the growth-promoting effect of adult tissue extracts on cell colonies *in vitro*, it became obvious that a starting material combining the characteristics of stability, uniformity, and easy sterilizability would facilitate the continuation of the work and obviate the tedious necessity of preparing extract under sterile conditions, from freshly removed tissue, each time a new experiment was contemplated. Acetone-desiccated adult chicken hearts were found to constitute such a material.

The procedure used was as follows: Hearts of adult chickens were packed in ice and sent to the laboratory as soon as convenient. Following gross dissection in order to remove the large vessels and fat tissue, the hearts were "homogenized" in a blender with as little physiological saline solution as possible to allow for smooth running of the machine, and the resulting mash was mixed with five times its weight of acetone, previously cooled in the icebox. The mixture was left in the icebox

<sup>1</sup> All expenses in connection with this work were borne by the British Empire Cancer Campaign.

for 30 minutes, rapidly filtered with suction on a Buchner funnel, washed with a little cold acetone, and again extracted for 30 minutes with acetone, using in this and in all the following extractions a weight of acetone equal to the weight of the original batch of hearts. In all, four extractions were made. After the final extraction the material was ground in a mortar, spread out on an evaporating dish, and freed of the last traces of acetone and water by keeping it from 24 to 48 hours in a large, evacuated desiccator, over  $\text{CaCl}_2$  or  $\text{H}_2\text{SO}_4$ .

The yield of dry substance is about 18 per cent of the weight of the fresh hearts used. The material is a very light, tawny-colored powder containing many fibers that remain unpowdered.

For the purpose of sterilization the powder was transferred, in amounts of 1-2 grams, to sterile, large, cork-stoppered centrifuge tubes, the tubes filled with acetone for 1-2 hours, and centrifuged. The excess acetone was pipetted off under sterile conditions and the tubes left overnight in a desiccator *in vacuo* to get rid of the acetone. The powder was then transferred with sterile precautions to ampoules which were sealed *in vacuo* and kept in the icebox.

Whenever heart extract is required, a sample of the powder is extracted for 24 hours, with 22 volumes of Tyrode's solution diluted with enough distilled water to obtain a final isotonic extract. In this way an extract is obtained which in its water content corresponds to that from an equivalent weight of fresh hearts made by our standard method (2). The extract from the dried powder, just as the fresh extract (1), can be diluted with an equal volume of Tyrode's solution without apparently diminishing its growth-promoting effect on cell colonies.

TABLE 1

COMPARISON OF THE SIZES OF CULTURE (MM.<sup>2</sup>) GROWN FOR SIX DAYS IN THE PRESENCE OF AN EXTRACT OF ACETONE-DESICCATED CHICKEN HEARTS (A) AND IN A PROTECTIVE MEDIUM (TYRODE'S SOLUTION) (B)

No. of culture	A	B
12203	97	8
12204	100	7
12221	96	5
12222	88	4
12223	96	13
12224	134	20
Average.....	101.8	9.5

The tests of growth-promoting power of the extract from acetone-desiccated tissue powder were made on standardized cultures of fibroblasts in Carrel flasks. The solid phase of the medium consisted of 0.5 ml. of chicken plasma and 1 ml. of Tyrode's solution coagulated with 1 drop of dilute embryo extract, while the liquid phase consisted of 1 ml. of the solution to be tested. The tests were always performed by comparing the growth of the two sister halves of a single standard culture.

It was found that the extract from the acetone dried heart powder has intense cell growth-promoting power, producing cultures with areas about 10 times as large as those of cultures growing in a protective medium (plasma + Tyrode's solution) (Table 1). A comparison of the growth-promoting effect of this extract with that of fresh adult heart extract, using both

in standard concentrations, shows that the former is somewhat more potent (Table 2).

TABLE 2

COMPARISON OF THE SIZES OF CULTURE (MM.<sup>2</sup>) GROWN FOR SIX DAYS IN THE PRESENCE OF AN EXTRACT OF ACETONE-DESICCATED CHICKEN HEARTS (A) AND AN EXTRACT OF FRESH CHICKEN HEARTS (B)

No. of culture	A	B
12205	80	40
12206	92	50
12209	80	96
12210	114	105
12225	94	50
12226	80	68
12337	115	72
12338	116	65
12341	96	88
12342	88	58
12375	63	52
12376	80	72
12379	51	64
12380	45	58
Average.....	85.3	67.0

Samples of acetone-desiccated chicken hearts have now been kept for five months and still fully retain their original activity.

An identical procedure performed on adult chicken brains has yielded a dried brain powder giving an extract with the same cell growth-promoting properties as extracts of the original brain tissue.

Acetone desiccation of pulped chicken embryos of various ages (8-18 days of incubation) has also yielded a dried powder which provides a growth-promoting extract as active as fresh chicken embryo extract made from the corresponding amount of fresh embryos.

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## Oral Administration of Small Doses of Liquids to Laboratory Animals

C. A. CABELL

Bureau of Animal Industry, Agricultural Research Administration, U. S. Department of Agriculture, Washington, D. C.

The problem of feeding small quantities of substances, especially liquids, to laboratory animals is of importance in many experimental procedures. Feeding from dishes has certain undesirable features, such as failure of animals to consume the dose completely and exposure of the material to destructive and contaminating effects.

Stomach-tube feeding as described by Marks (2) and recently by Lehr (1) is used widely but has some disadvantages. Considerable experience and skill are necessary with metal-type tubes to avoid injury to animals. Rubber tubes are sometimes cut by animals' teeth, and slight pressure on rubber and

silk tubes results in variation in the amount of material delivered. This is especially undesirable when small amounts of relatively concentrated solutions are being fed. Lehr has discussed the disadvantages of using the wooden, central-hole mouth gag.

The apparatus described here is simple to assemble from parts available in most any animal laboratory. Experience has shown it to be efficient and useful in feeding certain types of solutions, such as oil solutions of carotene and vitamin A. It is adapted especially to feeding small doses when relatively accurate measurement is required.

The apparatus (Fig. 1) consists of a ring stand on which is mounted an ordinary test tube holder in which is fastened a "tuberculin" syringe. Below this a blunt dissecting forceps is clamped in position so that the end of the syringe needle is directly above (about  $\frac{1}{4}$  inch). Obviously, a "hairpin" type of

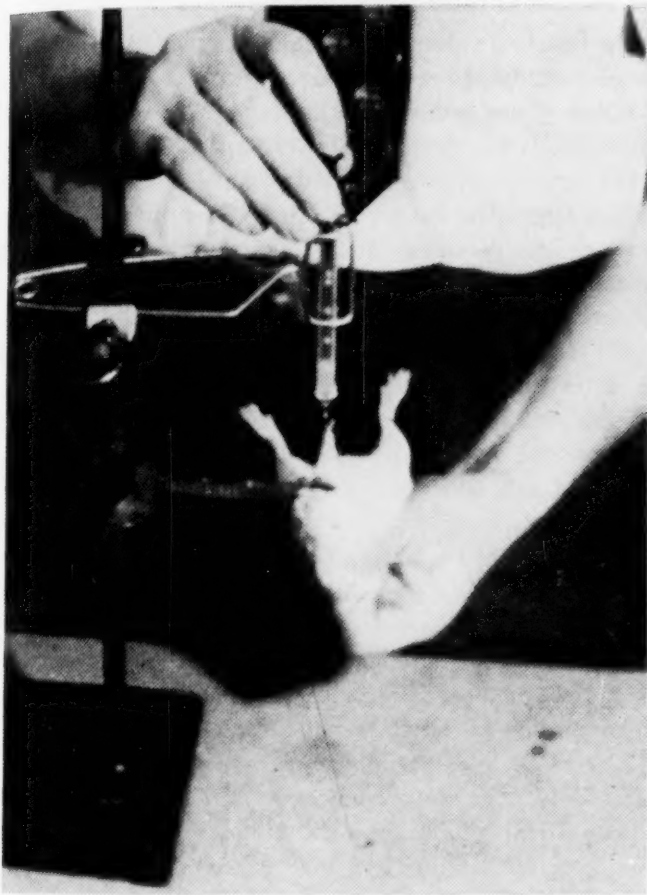


FIG. 1. Apparatus for drop feeding rats without assistance.

gag made from wire or small-diameter glass rod may be substituted for the forceps. However, the forceps has proved to be more satisfactory. Tension can be varied so that it can be adjusted to fit into the mouth of any size rat by adjusting the screw of the ordinary clamp holder, fastening it in position (Fig. 1).

In feeding animals the syringe is filled with the desired quantity of material and placed in the test-tube holder. The animal is grasped with the left hand; ample amounts of skin from the neck and back are held as shown in Fig. 1. With aid of the right hand the forceps is inserted in the animal's mouth. The right hand is then moved to operate the syringe and the feeding is dropped into the open mouth. Fig. 2 illustrates how the tongue should be held with forceps in order to produce a proper opening to receive the liquid. The animal can be immobilized by wrapping in a small towel (1), but this is not

necessary with the strain of rats used in this laboratory. If the neck skin is held with a firm grasp and the forceps inserted carefully to avoid hurting, there is no inclination on the part of the animal to struggle. The rat invariably swallows the solutions without ejecting them from its mouth. Many substances which the animal will not consume voluntarily can be fed in this manner.

Solutions may be fed as measured by calibration marks on the syringe, or drop weights may be calibrated. Although drop weight is affected by many variables, such as temperature of solution, time required for formation of drops and angle of needle, these factors can be standardized closely enough to insure uniform results. It will be found that counting a given number of standardized drops offers certain advantages in speed and accuracy in some feeding problems. Incidentally, clamping of the syringe in a vertical position, as shown in the figure, eliminates the variable due to holding the needle at different angles while feeding drops.

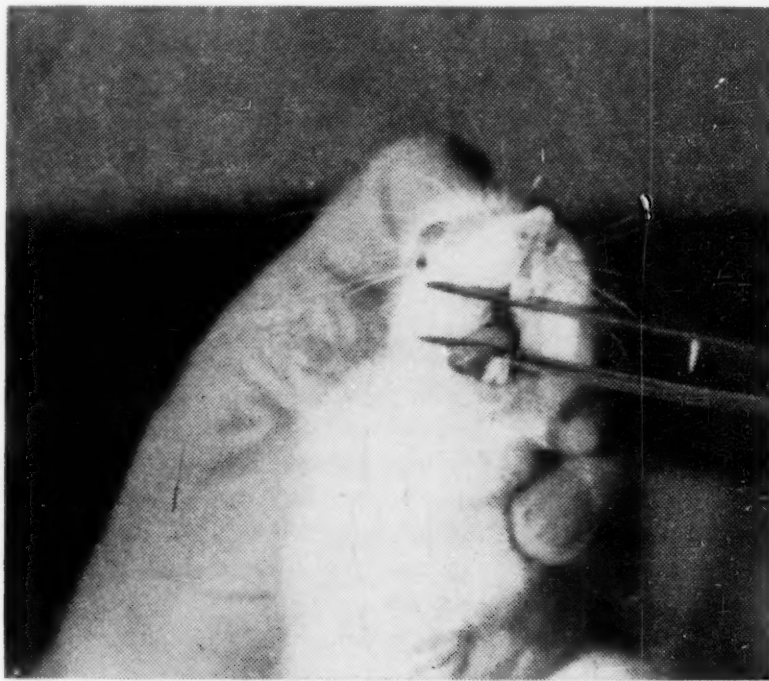


FIG. 2. Position of forceps for drop feeding.

Variation in size of drops can be controlled by using different size needles. The use of a timer with a long sweeping second hand is desirable to standardize timing of drops.

Concentrated solutions make smaller feedings possible and eliminate continual filling of the syringe. Very rapid feeding is possible, especially if the solutions fed are relatively concentrated. For instance, it has been found that an operator can remove an animal from its cage, feed 1-3 drops of solution, and return the animal to its cage in 10 seconds. This is probably faster than would be the case in actual practice, but it gives some idea of what can be expected when using the procedure.

The most desirable feature of the apparatus is that the necessity of an assistant for holding animals is entirely eliminated. One operator can work practically as fast as two, without sacrifice of accuracy or damage to the animals.

#### References

1. LEHR, D. *J. lab. clin. Med.*, 1945, 30, 977.
2. MARKS, L. H. *J. exp. Med.*, 1908, 10, 204.

# Book Reviews

**Trace elements in plants and animals.** Walter Stiles. Cambridge, Engl.: at the Univ. Press; New York: Macmillan, 1946. Pp. xi+189. (Illustrated.) \$2.75.

In the past two decades a tremendous literature has been amassed around the subject of so-called trace elements in soil-plant-animal interrelations. A recent compilation of abstracts includes over 7,000 references to published articles. Different as the approaches and points of view of these diverse publications are, they deal with several inorganic elements, all of which are involved in the economy of the living organism in very minute amounts.

It scarcely requires mention that so vast a literature is hardly manageable not only by the student of general plant and animal physiology but even by many workers in the field. Prof. Stiles has attempted to prepare within the limits of a small monograph, a digest of the significant developments in this field of knowledge. He has succeeded admirably in this undertaking and has produced a concise and lucid review of the salient facts underlying both the laboratory and the field aspects of the subject.

Following an historical introduction, thorough treatment is given analytical methods and nutrient culture procedures, so crucial in a field of experimentation in which micrograms and parts per billion are common units of measurement and distilled water and CP chemicals are almost invariably "contaminated" and cannot be used without further purification. The author has wisely stressed principles rather than minutiae of procedure, yet his discussion is thorough. In discussing micronutrient deficiency diseases of plants, individual sections are devoted to manganese, zinc, boron, copper, and molybdenum. In the chapter on animal nutrition, attention is given to disturbances traceable to either excess or deficiency of an element. Considerable space is assigned to the functional aspects of micronutrients as reflected by reciprocal relations of different nutrients. An extensive, yet selective, list of references is appended.

The discussion of functional aspects reflects the inadequate state of knowledge of this phase of the subject. Whatever precise information is available comes from the enzyme chemists concerned with metalloproteins. More generous treatment could have been given to the copper enzymes, with a discussion of laccase and ascorbic acid oxidase. The author, however, seems to have in general placed the biochemical aspects of the subject beyond the scope of the monograph.

It would be unreasonable to expect more material within the covers of so small a volume, yet the reviewer cannot refrain from wishing the author had considered some criteria for including a given element in the list of essential nutrients. Proposals will, no doubt, be made in the future for enlarging the list of essential elements, and the judicious evaluation of evidence in the light of some definite criteria of essentiality would be helpful.

These remarks are in no way intended to detract from the value of the book to investigators and students of soil science

and plant and animal physiology. The monograph should also prove of importance to biochemists as a useful and concise review of interesting problems in inorganic nutrition which as yet await elucidation.

DANIEL I. ARNON

*Division of Plant Nutrition, University of California, Berkeley*

**Gall midges of economic importance.** H. F. Barnes. London: Crosby Lockwood, 1946. Vol. I: Pp. 104; Vol. II: Pp. 160. (Illustrated.) 12/6 and 15/-.

These first two volumes of a series designed to cover a comprehensive study of the gall midges of the world are subtitled *Gall midges of root and vegetable crops* and *Gall midges of fodder crops*, respectively. Volume III, *Gall midges of fruit*, and Volume IV, *Gall midges of ornamental plants and shrubs*, are to be published later. The author also projects subsequent volumes on gall midges of trees, cereals, weeds, miscellaneous crops such as beverage plants and herbs, and midges which are zoophagous and fungivorous.

C. T. Gimingham, of Harpenden, gives a foreword to the series in the first volume, and each volume has a special introduction as well as a very complete list of the literature of the subject matter, which is materially enhanced in usefulness by an index to gall midge names, a plant index, and a general index. Over 60 species of midges are covered in the first volume, while more than 160 species are included in the second. The writing is smooth and pleasant, making the books very readable. Each volume is complete in itself.

Gall midges include such insects as the Hessian fly, chrysanthemum midge, pear midge, clover seed midge, and many other important midge pests which the author still recognizes as the Cecidomyiidae but which in America we generally term the Itonididae. Generally speaking, the family is herbivorous, but a considerable number of the species are zoophagous.

The material is arranged under the food plants, which appear in alphabetical order. Although the less important insects are not set off distinctly, the index helps to overcome this difficulty. This fault, however, makes the books less valuable as a reference work. The arrangement of items under the important species of insects is excellent. First, there is a paragraph on diagnostic characters, which is followed, in order, by a general description, a complete distribution, and paragraphs on life history, food plants, natural enemies, and control. The author closes each volume with a reference to specimen material used and cites the more important literature relating to the species.

There are a number of illustrations, mostly photographic, with some colored plates, but these do not add much to this excellent work. Barnes has brought together a wealth of information in a group generally neglected by economic entomologists, and his work should be a stimulus to others to investigate the Itonididae.

JAMES A. HYSLOP

*Silver Spring, Maryland*